The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

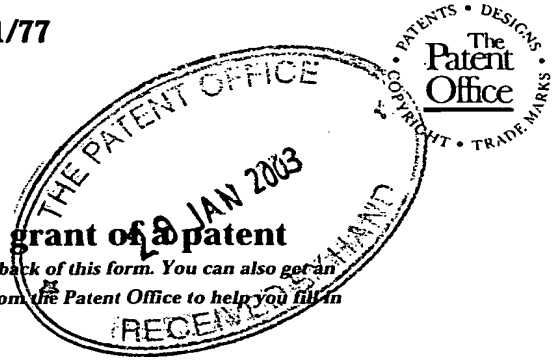
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed P. Mahoney

Dated 28 November 2003

Patents Form 1/77

Pat[redacted]t 1977
([redacted])



30JAN03 E780941-25 D00060
P01/7700 0.00-0302094.8

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference — RJW/CP6107890

2. Patent application number *(The Patent Office will fill in this part)* — 29 JAN 2003 — 0302094.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PHARMAGENE LABORATORIES LIMITED
2 Orchard Road
Royston
HERTS SG8 5HD

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — ENGLAND

7285178001

4. Title of the invention — EP4 RECEPTOR ANTAGONISTS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP

Patents ADP number *(if you know it)* — 109006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	94
Claim *(s)*	5
Abstract	0
Drawing *(s)*	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 29 January 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

ROBERT WATSON
020 7240 4405

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

EP_4 RECEPTOR ANTAGONISTS

This invention relates to EP_4 receptor antagonists, pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions to treat various diseases.

Background to the invention

Prostanoids comprise prostaglandins (PGs) and thromboxanes (Txs) and their receptors fall into five different classes (DP, EP, FP, IP and TP) based on their sensitivity to the five naturally occurring prostanoids, PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and TxA_2, respectively (Coleman, R.A., Prostanoid Receptors. *IUPHAR compendium of receptor characterisation and classification*, 2nd edition, 338-353, ISBN 0-9533510-3-3, 2000). EP receptors (for which the endogenous ligand is PGE_2) have been subdivided into four types termed EP_1, EP_2, EP_3 and EP_4. These four types of EP receptors have been cloned and are distinct at both a molecular and pharmacological level (Coleman, R.A., 2000)

EP_4 antagonists have been shown to be useful in the treatment of pain, and in particular, in the treatment of primary headache disorders, which include migraines, and drug-induced headaches (WO 00/18405 and WO 01/72302). Dilation of the cerebral vasculature and the subsequent stimulation of pain stimulating, perivascular trigeminal sensory afferent nerves is recognised to play an important role in the pathophysiology of migraine. A sterile inflammatory response, associated with activation of cycloxygenase and the generation of PGE_2, is also implicated in the pathophysiology of migraine. PGE_2 levels have been shown to be raised during migraine attacks and PGE_2 contributes to the pain of migraine by directly dilating

cerebral arteries and by stimulating the release of vasoactive/pro-inflammatory peptides from the trigeminal nerves. These effects of PGE_2 are mediated in whole or in part by EP_4 receptors. Thus, by binding to and preventing the stimulation of EP_4 receptors, EP_4 antagonists may be used to treat the pain of migraine.

EP_4 antagonists may also be useful in treating a number of other conditions and diseases. For example, they may be used in:

the treatment of pain associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis;

the treatment of musculoskeletal pain, lower back and neck pain, sprains and strains, neuropathic pain, sympathetically mediated pain, myositis, pain associated with cancer and fibromyalgia, pain associated with influenza or other viral infections, such as the common cold, rheumatic fever; pain associated with bowel disorders such as non-ulcer dyspepsia, irritable bowel syndrome; non-cardiac chest pain, pain associated with myocardial ischaemia, post-operative pain, headache, toothache and dysmenorrhea. Neuropathic pain syndromes include diabetic neuropathy, sciatica, non-specific lower back pain, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, trigeminal neuralgia and pain resulting from physical trauma;

the treatment of inflammatory diseases including rheumatoid and osteoarthritis, psoriasis, dermatitis, retinitis, conjunctivitis, asthma, bronchitis, chronic obstructive pulmonary disease, inflammatory bowel disease, colitis, nephritis, gingivitis and hepatitis;

the treatment of cancers including familial adenomatous polyposis, endometrial carcinoma, colorectal and cervical

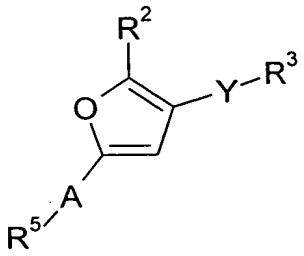
cancer;
the treatment of bone disorders involving altered bone formation or resorption such as osteoporosis;
women's health for the treatment of myometrial and endometrial disorders;
the treatment of gastrointestinal disease including diarrhoea;
the treatment of immunological disorders such as autoimmune disease, immunological deficiency diseases, organ transplantation and increasing the latency of HIV infection;
the treatment of diseases of abnormal platelet function. (e.g. occlusive vascular diseases);
the preparation of a drug with diuretic properties to treat or prevent various oedema, hypertension, premenstrual tension, urinary calculus, oliguria, hyperphosphaturia, mesangial proliferative glomerulonephritis, chronic renal failure or the like;
the treatment of impotence or erectile dysfunction, and female sexual dysfunction;
the treatment of hair growth disorders;
the treatment of sleep disorders such as narcolepsy and insomnia;
the treatment of cardiovascular diseases and shock states associated with hypotension (e.g. septic shock);
the treatment of neurodegenerative diseases and for preventing neuronal damage following stroke, cardiac arrest, cardiopulmonary bypass, traumatic brain injury or spinal cord injury;
the treatment of tinnitus;
the treatment of dependence; and
the treatment of complications of diabetes.

Although EP_4 antagonists are known, it is desired to find novel EP_4 antagonists, and in particular, EP_4 antagonists

which are selective against other EP receptors, i.e. EP_1, EP_2 and EP_3.

Summary of the invention

A first aspect of the present invention provides a compound of formula (**I**):



(I)

or a pharmaceutically acceptable salt thereof for use in a method of therapy, wherein:

R^2 is H or an optionally substituted C_{1-4} alkyl group;

Y is either $-(CH_2)_n-O-$, where n is 1 or 2, or $-C(=O)NR^N-$, where R^N is selected from H, and optionally substituted C_{1-7} alkyl or C_{5-20} aryl;

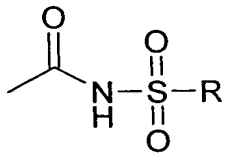
R^3 is an optionally substituted C_6 aryl group linked to a further optionally substituted C_6 aryl group, wherein if both C_6 aryl groups are benzene rings, there may be an oxygen bridge between the two rings, bound adjacent the link on both rings;

A is a single bond or a C_{1-3} alkylene group; and

R^5 is either:

(i) carboxy;

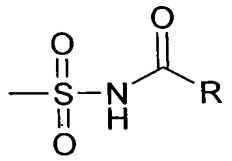
(ii) a group of formula (**II**):



(II)

; or

(iii) a group of formula (**III**):

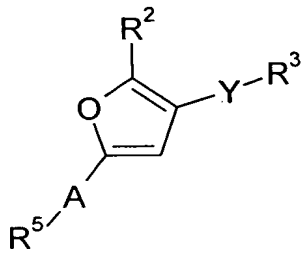


(**III**)

,

wherein R is optionally substituted C_{1-7} alkyl or C_{5-20} aryl.

A second aspect of the present invention provides a compound of formula (**I**):



(**I**)

or a salt, solvate and chemically protected form thereof, wherein:

R^2 is H or an optionally substituted C_{1-4} alkyl group;

Y is either $-(CH_2)_n-O-$, where n is 1 or 2, or $-C(=O)NR^N-$, where R^N is selected from H, and optionally substituted C_{1-7} alkyl or C_{5-20} aryl;

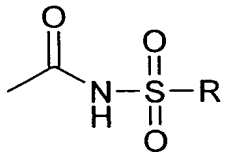
R^3 is an optionally substituted C_6 aryl group linked to a further optionally substituted C_6 aryl group, wherein if both C_6 aryl groups are benzene rings, there may be an oxygen bridge between the two rings, bound adjacent the link on both rings;

A is a single bond or a C_{1-3} alkylene group; and

R^5 is either:

(i) carboxy;

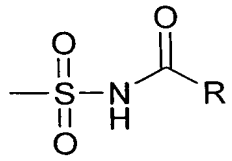
(ii) a group of formula (**II**):



(**II**)

; or

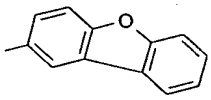
(iii) a group of formula (**III**):

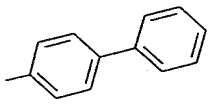


(III)

,

wherein R is optionally substituted C_{1-7} alkyl or C_{5-20} aryl, except that when R^2 is methyl, Y is $-CH_2-O-$ and R^5 is carboxy or C_{1-7} alkyl ester thereof, then R^3 is not:

(i)  ; or

(ii) 

A third aspect of the present invention provides a pharmaceutical composition comprising a compound of formula (**I**) as defined in the first aspect or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

A further aspect of the present invention provides the use of a compound of formula (**I**) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by antagonism of an EP_4 receptor.

Another aspect of the present invention provides a method of treating a condition which can be alleviated by antagonism of an EP_4 receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula (**I**), or a pharmaceutically acceptable salt thereof.

Conditions which can be alleviated by antagonism of an EP_4 receptor are discussed above, and particularly include primary headache disorders, most particularly migraines.

The present invention also provides methods of antagonizing EP_4 receptors, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of formula (**I**).

In some embodiments, the compounds described above may be selective as against antagonism of the other three EP receptors, i.e. EP_1, EP_2 and EP_3. This selectivity allows for targeting of the effect of the compounds of the invention, with possible benefits in the treatment of certain conditions.

Definitions

Monodentate groups

(i.e groups with one point of covalent attachment)

Alkyl: The term "alkyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 7 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated or unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cylcoalkynyl, etc., discussed below.

In the context of alkyl groups, the prefixes (e.g. C_{1-4}, C_{1-7}) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C_{1-4} alkyl" as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C_{1-4} alkyl ("lower alkyl")and C_{1-7} alkyl. Note that the first prefix

may vary according to other limitations; for example, for unsaturated alkyl groups, the first prefix must be at least 2; for cyclic alkyl groups, the first prefix must be at least 3; etc.

Examples of saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4), pentyl (C_5), hexyl (C_6) and heptyl (C_7).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6), and n-heptyl (C_7).

Examples of saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

Alkenyl: The term "alkenyl" as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds. Examples of groups of alkenyl groups include C_{2-4} alkenyl and C_{2-7} alkenyl. Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl, $-CH=CH_2$), 1-propenyl ($-CH=CH-CH_3$), 2-propenyl (allyl, $-CH-CH=CH_2$), isopropenyl (1-methylvinyl, $-C(CH_3)=CH_2$), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

Alkynyl: The term "alkynyl" as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C_{2-4} alkynyl and C_{2-7} alkynyl. Examples of alkynyl groups include, but are not limited to, ethynyl (ethinyl, $-C\equiv CH$) and 2-propynyl (propargyl, $-CH_2-C\equiv CH$).

Cycloalkyl: The term "cycloalkyl" as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a carbocyclic ring of a carbocyclic compound, which carbocyclic ring may be saturated or unsaturated, which moiety has from 3 to 7 carbon atoms (unless otherwise specified), including from 3 to 7 ring atoms. Thus, the term "cycloalkyl" includes the sub-classes cycloalkyenyl and cycloalkynyl. Preferably, each ring has from 3 to 7 ring atoms. Examples of groups of cycloalkyl groups include C_{3-7} cycloalkyl.

Examples of cycloalkyl groups include, but are not limited to, those derived from:

saturated monocyclic hydrocarbon compounds: cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), cycloheptane (C_7), methylcyclopropane (C_4), dimethylcyclopropane (C_5), methylcyclobutane (C_5), dimethylcyclobutane (C_6), methylcyclopentane (C_6), dimethylcyclopentane (C_7), methylcyclohexane (C_7);

unsaturated monocyclic hydrocarbon compounds: cyclopropene (C_3), cyclobutene (C_4), cyclopentene (C_5), cyclohexene (C_6), methylcyclopropene (C_4), dimethylcyclopropene (C_5), methylcyclobutene (C_5), dimethylcyclobutene (C_6), methylcyclopentene (C_6), dimethylcyclopentene (C_7), methylcyclohexene (C_7);

Heterocyclyl: The term "heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g. C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6} heterocyclyl" as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C_{3-20} heterocyclyl, C_{5-20} heterocyclyl, C_{3-15} heterocyclyl, C_{5-15} heterocyclyl, C_{3-12} heterocyclyl, C_{5-12} heterocyclyl, C_{3-10} heterocyclyl, C_{5-10} heterocyclyl, C_{3-7} heterocyclyl, C_{5-7} heterocyclyl, and C_{5-6} heterocyclyl.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);

O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);

S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);

O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);

O_3: trioxane (C_6);

N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);

N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);
N_2O_1: oxadiazine (C_6);
O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,
$N_1O_1S_1$: oxathiazine (C_6).

Aryl: The term "aryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms.

In this context, the prefixes (e.g. C_{3-20}, C_{5-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6} aryl" as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C_{3-20} aryl, C_{5-20} aryl, C_{5-15} aryl, C_{5-12} aryl, C_{5-10} aryl, C_{5-7} aryl, C_{5-6} aryl, C_5 aryl, and C_6 aryl.

The ring atoms may be all carbon atoms, as in "carboaryl groups". Examples of carboaryl groups include C_{3-20} carboaryl, C_{5-20} carboaryl, C_{5-15} carboaryl, C_{5-12} carboaryl, C_{5-10} carboaryl, C_{5-7} carboaryl, C_{5-6} carboaryl, C_5 carboaryl, and C_6 carboaryl.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e. phenyl) (C_6), naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indane (e.g., 2,3-dihydro-

1H-indene) (C_9), indene (C_9), isoindene (C_9), tetraline (1,2,3,4-tetrahydronaphthalene (C_{10}), acenaphthene (C_{12}), fluorene (C_{13}), phenalene (C_{13}), acephenanthrene (C_{15}), and aceanthrene (C_{16}).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups". Examples of heteroaryl groups include C_{3-20} heteroaryl, C_{5-20} heteroaryl, C_{5-15} heteroaryl, C_{5-12} heteroaryl, C_{5-10} heteroaryl, C_{5-7} heteroaryl, C_{5-6} heteroaryl, C_5 heteroaryl, and C_6 heteroaryl.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:
N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);
O_1: furan (oxole) (C_5);
S_1: thiophene (thiole) (C_5);
N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);
N_2O_1: oxadiazole (furazan) (C_5);
N_3O_1: oxatriazole (C_5);
N_1S_1: thiazole (C_5), isothiazole (C_5);
N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6), pyrazine (1,4-diazine) (C_6);
N_3: triazole (C_5), triazine (C_6); and,
N_4: tetrazole (C_5).

Examples of heteroaryl groups which comprise fused rings, include, but are not limited to:

C_9 (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), indolizine (N_1), indoline (N_1), isoindoline (N_1), purine (N_4) (e.g., adenine, guanine), benzimidazole (N_2), indazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2),

benzofurazan (N_2O_1), benzotriazole (N_3), benzothiofuran (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

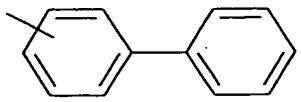
C_{10} (with 2 fused rings) derived from chromene (O_1), isochromene (O_1), chroman (O_1), isochroman (O_1), benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), quinolizine (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2), quinoxaline (N_2), quinazoline (N_2), cinnoline (N_2), phthalazine (N_2), naphthyridine (N_2), pteridine (N_4);

C_{11} (with 2 fused rings) derived from benzodiazepine (N_2);

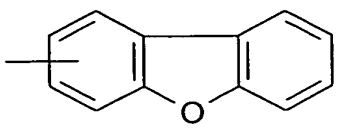
C_{13} (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1), carboline (N_2), perimidine (N_2), pyridoindole (N_2); and,

C_{14} (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), thioxanthene (S_1), oxanthrene (O_2), phenoxathiin (O_1S_1), phenazine (N_2), phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

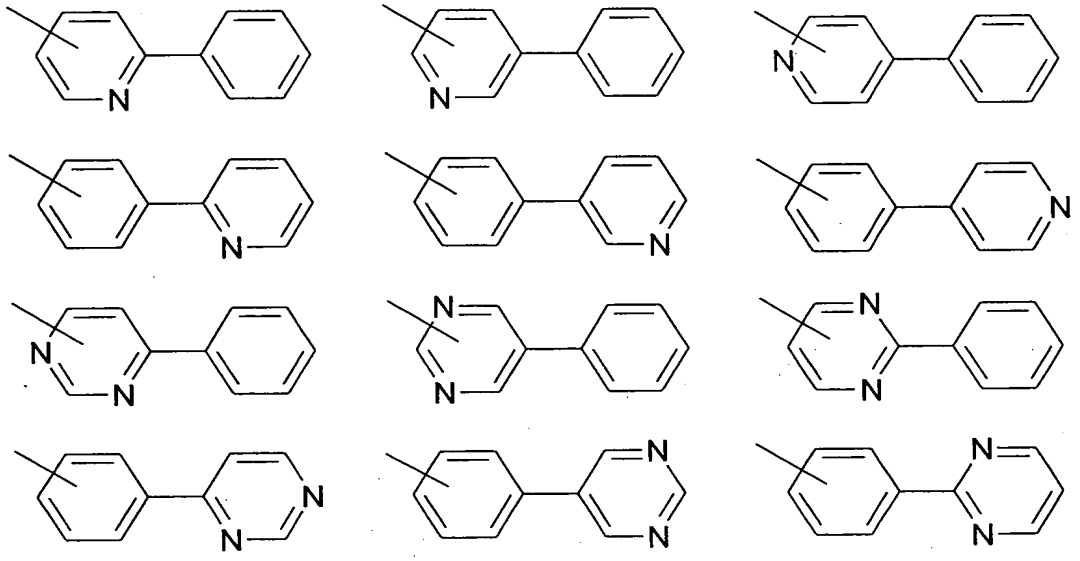
R^3 is defined above as an optionally substituted C_6 aryl group linked to a further optionally substituted C_6 aryl group, wherein if both C_6 aryl groups are benzene rings , there may be an oxygen bridge between the two rings, bound adjacent the link on both rings. Thus, if both C_6 aryl groups are benzene rings, then R^3 can be optionally subtitued biphenyl:



or optionally substituted dibenzofuran:



If one of the C_6 aryl groups is a C_6 heteroaryl group, then examples of R^3 include, but are not limited to (not showing optional substitution):



The above groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves, the additional monodentate substituents listed below and alkoxylene.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkoxy group, discussed below), a C_{3-20} heterocyclyl group (also referred to as a C_{3-20} heterocyclyloxy group), or a C_{5-20} aryl group (also referred to as a C_{5-20} aryloxy group), preferably a C_{1-7} alkyl group.

C_{1-7} alkoxy: -OR, wherein R is a C_{1-7} alkyl group. Examples of C_{1-7} alkoxy groups include, but are not limited to, -OMe

(methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

Oxo (keto, -one): =O.

Thione (thioketone): =S.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of imino groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylacyl or C_{1-7} alkanoyl), a C_{3-20} heterocyclyl group (also referred to as C_{3-20} heterocyclylacyl), or a C_{5-20} aryl group (also referred to as C_{5-20} arylacyl), preferably a C_{1-7} alkyl group. Examples of acyl groups include, but are not limited to, $-C(=O)CH_3$ (acetyl), $-C(=O)CH_2CH_3$ (propionyl), $-C(=O)C(CH_3)_3$ (t-butyryl), and -C(=O)Ph (benzoyl, phenone).

Carboxy (carboxylic acid): -C(=O)OH.

Thiocarboxy (thiocarboxylic acid): -C(=S)SH.

Thiolocarboxy (thiolocarboxylic acid): -C(=O)SH.

Thionocarboxy (thionocarboxylic acid): -C(=S)OH.

Imidic acid: -C(=NH)OH.

Hydroxamic acid: -C(=NOH)OH.

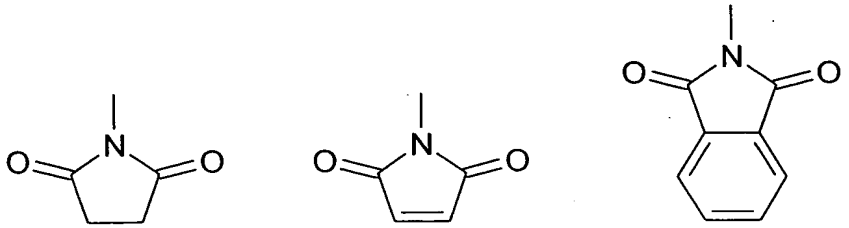
Ester (carboxylate, carboxylic acid ester, oxycarbonyl): -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh.

Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, -OC(=O)Ph, and $-OC(=O)CH_2Ph$.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_2CH_3$, and $-C(=O)N(CH_2CH_3)_2$, as well as amido groups in which R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

Acylamido (acylamino): $-NR^1C(=O)R^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably

hydrogen or a C_{1-7} alkyl group. Examples of acylamide groups include, but are not limited to, $-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, and $-NHC(=O)Ph$. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:

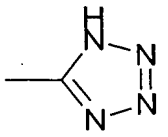


Thioamido (thiocarbamyl): $-C(=S)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of thioamido groups include, but are not limited to, $-C(=S)NH_2$, $-C(=S)NHCH_3$, $-C(=S)N(CH_3)_2$, and $-C(=S)NHCH_2CH_3$.

Ureido: $-N(R^1)CONR^2R^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R^1 is a ureido substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of ureido groups include, but are not limited to, $-NHCONH_2$, -NHCONHMe, -NHCONHEt, $-NHCONMe_2$, $-NHCONEt_2$, $-NMeCONH_2$, -NMeCONHMe, -NMeCONHEt, $-NMeCONMe_2$, and $-NMeCONEt_2$.

Guanidino: $-NH-C(=NH)NH_2$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di-C_{1-7} alkylamino), a C_{3-20} heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7} alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ($-NH_2$), secondary ($-NHR^1$), or tertiary ($-NHR^1R^2$), and in cationic form, may be quaternary ($-^+NR^1R^2R^3$). Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHC(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

Amidine (amidino): $-C(=NR)NR_2$, wherein each R is an amidine substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group. Examples of amidine groups include, but are not limited to, $-C(=NH)NH_2$, $-C(=NH)NMe_2$, and $-C(=NMe)NMe_2$.

Nitro: $-NO_2$.

Nitroso: -NO.

Cyano (nitrile, carbonitrile): -CN.

Sulfhydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkylthio group), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of C_{1-7} alkylthio groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

Disulfide: -SS-R, wherein R is a disulfide substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group (also referred to herein as C_{1-7} alkyl disulfide). Examples of C_{1-7} alkyl disulfide groups include, but are not limited to, $-SSCH_3$ and $-SSCH_2CH_3$.

Sulfine (sulfinyl, sulfoxide): $-S(=O)R$, wherein R is a sulfine substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfine groups include, but are not limited to, $-S(=O)CH_3$ and $-S(=O)CH_2CH_3$.

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group, including, for example, a fluorinated or perfluorinated C_{1-7} alkyl group. Examples of sulfone groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$ (triflyl), $-S(=O)_2CH_2CH_3$ (esyl), $-S(=O)_2C_4F_9$ (nonaflyl), $-S(=O)_2CH_2CF_3$ (tresyl), $-S(=O)_2CH_2CH_2NH_2$ (tauryl), $-S(=O)_2Ph$ (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl

(nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

Sulfinic acid (sulfino): $-S(=O)OH$, $-SO_2H$.

Sulfonic acid (sulfo): $-S(=O)_2OH$, $-SO_3H$.

Sulfinate (sulfinic acid ester): $-S(=O)OR$; wherein R is a sulfinate substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinate groups include, but are not limited to, $-S(=O)OCH_3$ (methoxysulfinyl; methyl sulfinate) and $-S(=O)OCH_2CH_3$ (ethoxysulfinyl; ethyl sulfinate).

Sulfinyloxy: $-OS(=O)R$, wherein R is a sulfinyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide): $-S(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-S(=O)NH_2$, $-S(=O)NH(CH_3)$, $-S(=O)N(CH_3)_2$, $-S(=O)NH(CH_2CH_3)$, $-S(=O)N(CH_2CH_3)_2$, and $-S(=O)NHPh$.

Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide): $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$, $-S(=O)_2N(CH_2CH_3)_2$, and $-S(=O)_2NHPh$.

Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonamino groups include, but are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinamino groups include, but are not limited to, $-NHS(=O)CH_3$ and $-N(CH_3)S(=O)C_6H_5$.

As already mentioned, the above described groups may be substituted, and particular examples include, but are not limited to, C_{3-20} aryl-C_{1-7} alkyl groups, which include benzyl (phenylmethyl, $PhCH_2-$), benzhydryl (Ph_2CH-), trityl (triphenylmethyl, Ph_3C-), phenethyl (phenylethyl, $Ph-CH_2CH_2-$), styryl ($Ph-CH=CH-$) and cinnamyl ($Ph-CH=CH-CH_2-$).

Bidentate groups

(i.e. groups with two points of covalent attachment; linking groups)

Alkylene: The term "C_{1-3} alkylene", as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms from each of two different carbon atoms, of a linear hydrocarbon compound having from 1 to 3 carbon atoms, which may be saturated or unsaturated. Thus, the term "alkylene" includes the sub-classes alkenylene and alkynylene.

In this context, the prefix C_{1-3} denotes the number of carbon atoms, or range of number of carbon atoms.

Examples of saturated C_{1-3} alkylene groups include $-CH_2-$ (methylene), $-CH_2CH_2-$ (ethylene) and $-CH_2CH_2CH_2-$ (propylene).

Examples of unsaturated C_{1-3} alkylene groups (which may be termed "C_{2-3} alkenylene" or "C_{2-3} alkynylene", as appropriate) include -CH=CH- (vinylene), $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-$, $-C\equiv C-CH_2-$ and $-CH_2-C\equiv C-$.

The C_{1-3} alkylene group may be substituted by any monodentate substituent described above.

Alkoxylene: The term "alkoxylene," as used herein, pertains to a bidentate group of formula $-O(CH_2)_nO-$, where n is 1 or 2.

Includes Other Forms

Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

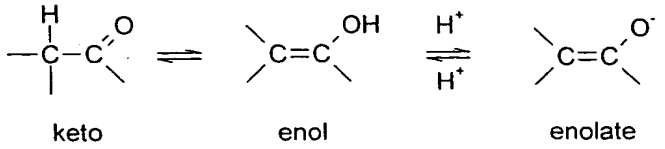
Isomers, Salts, Solvates and Protected Forms

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric

forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers", as used herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g. C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hyroxyazo, and nitro/aci-nitro.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g. fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge, *et al.*, *J. Pharm. Sci.*, **66**, 1-19 (1977).

For example, if the compound is anionic, or has a functional group which may be anionic (e.g. -COOH may be $-COO^-$), then a salt may be formed with a suitable cation. Examples of

suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e. NH_4^+) and substituted ammonium ions (e.g. NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g. $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to,

those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g. pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A wide variety of such "protecting", "blocking", or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>$C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide

(-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O·).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7} haloalkyl ester (e.g., a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7} alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester (e.g. a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether ($-S-CH_2NHC(=O)CH_3$).

The term "treatment", as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

The term "therapeutically-effective amount", as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable

benefit/risk ratio, when administered in accordance with a desired treatment regimen. Suitable dose ranges will typically be in the range of from 0.01 to 20 mg/kg/day, preferably from 0.1 to 10 mg/kg/day.

Compositions and their administration

Compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound as defined above may be formulated as suppositories using, for example, polyalkylene glycols, acetylated triglycerides and the like, as the carrier. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc, an active compound as defined above and optional pharmaceutical

adjuvants in a carrier, such as, for example, water, saline aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 20th edition, pub. Lippincott, Williams & Wilkins, 2000. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to alleviate the symptoms of the subject being treated.

Dosage forms or compositions containing active ingredient in the range of 0.25 to 95% with the balance made up from non-toxic carrier may be prepared.

For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, sodium crosscarmellose, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain 1%-95% active ingredient, more preferably 2-50%, most preferably 5-8%.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, triethanolamine sodium acetate, etc.

The percentage of active compound contained in such parental compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.1% to 10% in solution are employable, and will be higher if the composition is a solid which will be subsequently diluted to the above percentages. Preferably, the composition will comprise 0.2-2% of the active agent in solution.

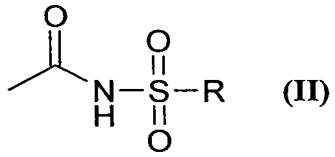
Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et_2O), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), acetonitrile (ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

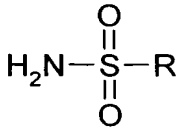
General Synthesis Methods

Compounds of the invention wherein R^5 is of formula (**II**):



(II)

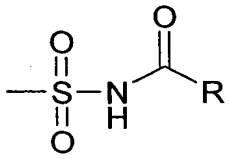
may be synthesised from the analogous compound of the invention wherein R^5 is carboxy, by reaction with a compound of formula 1:



Formula 1

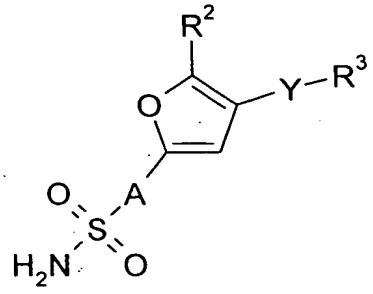
in basic conditions, preferably aided by a coupling agent, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

Compounds of the invention wherein R^5 is of formula (**III**):



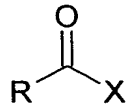
(III)

may be synthesized from a compound of formula 2:



Formula 2

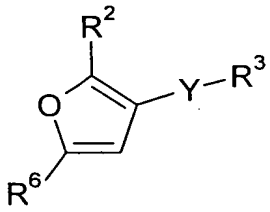
by reaction with a compound of formula 3:



Formula 3

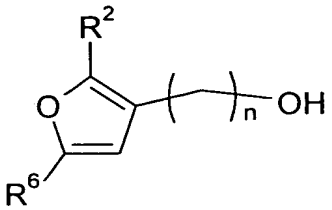
wherein X is either OH or halo, where if X is OH, the use of basic conditions and a coupling agent is preferred.

Compounds of formulae (**I**) and 2, or where the group $-A-R^5$ is present as a precursor or protected form, may be represented as compounds of formula 4:



Formula 4

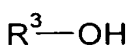
where R^6 is $-A-R^5$ or its precursor or protected form. The protecting groups used may be conventional, or the group may be resin-bound. If Y is $-(CH_2)_n-O-$, then these compounds can be synthesised from compounds of formula 5:



Formula 5

by one of two possible routes.

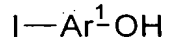
In the first route, a compound of formula 6:



Formula 6

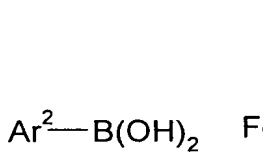
is coupled to a compound of formula 5 using the Mitsunobu reaction, for example by treatment with triphenyl phosphine (Ph_3P) and diisopropylazodicarboxylate (DIAD).

The second route is a two stage route, the first stage being the Mitsunobu coupling of a compound of formula 7a:

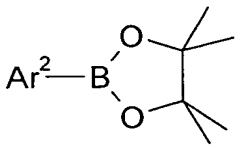


Formula 7a

wherein Ar^1 is the first C_6 aryl component of R^3, followed by a Suzuki coupling of a compound of formula 8a (or equivalent ester of formula 8c):



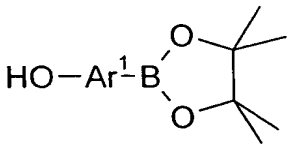
Formula 8a



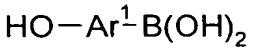
Formula 8c

wherein Ar^2 is the second C_6 aryl component of R^3. The Suzuki coupling may be achieved using, for example, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) as the palladium catalyst.

This route may also be 'reversed' such that the Mitsunobo coupling is of a boronic acid of formula 7b (or preferably equivalent ester of formula 7c):

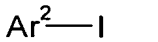


Formula 7c



Formula 7b

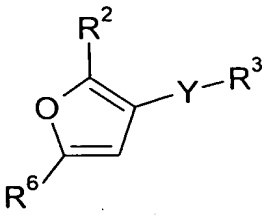
wherein Ar^1 is the first C_6 aryl component of R^3, followed by a Suzuki coupling of a compound of formula 8b:



Formula 8b

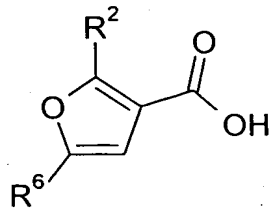
wherein Ar^2 is the second C_6 aryl component of R^3.

Compounds of formula 4:



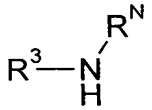
Formula 4

where Y is $-C(=O)-NR^N-$ may be synthesised from a compound of formula 9:



Formula 9

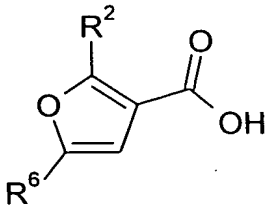
by reaction with a amine of formula 10:



Formula 10

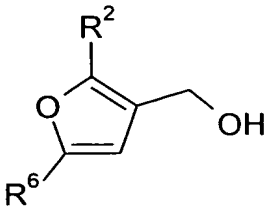
in basic conditions, preferably with the aid of a coupling agent.

Compounds of formula 9:



Formula 9

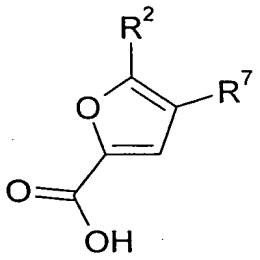
may be derived from compounds of formula 11:



Formula 11

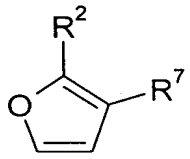
by oxidation, for example, using Jones' reagent.

Compounds of formula (**I**) where A is a single bond, and R^5 is carboxy, and compounds where the group $-Y-R^3$ is present as a precursor or protected form, may be represented as compounds of formula 12:



Formula 12

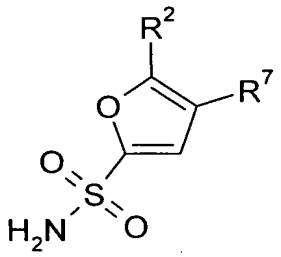
where R^7 is $-Y-R^3$ or its precursor or protected form. These compounds may be synthesised from compounds of formula 13:



Formula 13

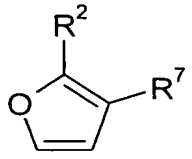
by treatment with a strong base and carbon dioxide at low temperatures.

In a similar fashion, compounds of formula 2 where A is a single bond, and R^5 is carboxy, and compounds where the group $-Y-R^3$ is present as a precursor or protected form, may be represented as compounds of formula 14:



Formula 14

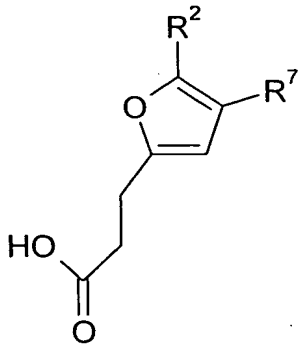
where R^7 is $-Y-R^3$ or its precursor or protected form. These compounds may be synthesised from compounds of formula 13:



Formula 13

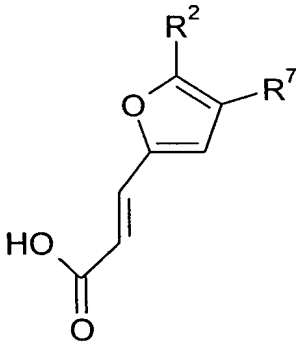
by treatment with a strong base and sulphur dioxide at low temperatures, followed by amination.

Compounds of formula (**I**) where A is a $-C_2H_4-$, and R^5 is carboxy, and compounds where the group $-Y-R^3$ is present as a precursor or protected form, may be represented as compounds of formula 15:



Formula 15

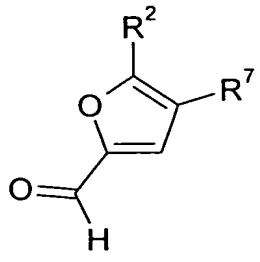
where R^7 is $-Y-R^3$ or its precursor or protected form. These compounds may be synthesised from compounds of formula 16:



Formula 16

by hydrogenation, using a palladium catalyst.

Compounds of formula 16 may be synthesised from compounds of formula 17:



Formula 17

by the Wittig coupling of an acetic ester, using, for example, triethylphosphonoacetate as the Wittig reagent, followed by hydolysis under alkaline conditions, e.g. lithium hydroxide in a suitable solvent, e.g. aqueous alcohol.

The starting materials described above are generally commercially available or synthesisable using known methods.

Preferences

The following preferences may be combined with one another, and may be different for each aspect of the present invention.

R^2 is preferably selected from H or an optionally substituted C_1 alkyl group, more preferably H or methyl, and most preferably R^2 is a a methyl group.

Y is preferably $-(CH_2)_n-O-$, and n is preferably 1, such that the most preferred option for Y is $-CH_2-O-$.

If Y is $-C(=O)NR^N-$, then R^N is preferably selected from H, and optionally substituted C_{1-4} alkyl, in particular Me.

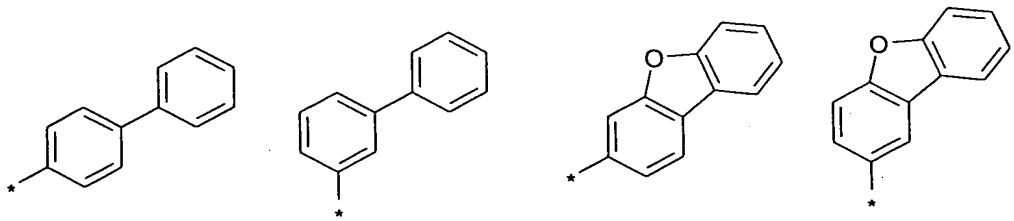
The C_6 aryl groups of R^3 are preferably independently selected from those derived from benzene and heteroaryl groups, where the heteroatom or heteroatoms are nitrogen. Most preferred are C_6 aryl groups derived from benzene and pyridine. It is further preferred that either both C_6 aryl groups are derived from benzene or that one group is derived from benzene and the other from pyridine.

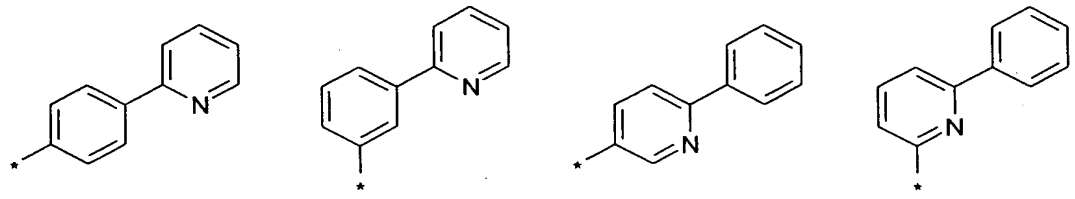
If both C_6 aryl groups are derived from benzene, it is preferred that there is not an oxygen bridge between the two

rings, bound adjacent the link on both rings, i.e. that R_3 is optionally substituted biphenyl rather than optionally substituted dibenzofuranyl.

If one or more of the C_6 aryl groups is derived from pyridine, then it is preferred that the nitrogen ring atom is adjacent the link between the two rings that make up the R^3 group.

It is further preferred that that the single bond joining the two C_6 aryl groups is in the 4-position of the ring bound to Y. Thus, 4-phenyl-phenyl is preferred to 3-phenyl-phenyl; dibenzofuran-3-yl is preferred to di-benzofuran-2-yl, 4-pyridin-2-yl-phenyl is preferred to 3-pyridin-2-yl-phenyl and 6-phenyl-pyridin-3-yl is preferred to 6-phenyl-pyridin-2-yl:





Both C_6 aryl groups of R^3 are optionally substituted, although it is preferred that only the C_6 aryl group not bound to Y is substituted.

Preferred substituents on the C_6 aryls of R^3 include, but are not limited to: optionally substituted C_{1-7} alkyl groups,

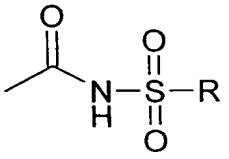
more preferably substituted C_{1-4} alkyl groups, e.g. $-CF_3$, CH_2OH; C_{1-7} alkoxy groups, more preferably C_{1-4} alkoxy groups, e.g. -OMe, $-OCF_3$, -OEt; C_{1-7} thioether group, more preferably C_{1-4} thioether group, e.g. -SMe; amino groups, optionally substituted by one or two C_{1-4} alkyl groups, e.g. $-NMe_2$; halo groups, more preferably -F or -Cl; cyano; alkoxylene groups, more preferably $-O-CH_2-O-$; C_{1-4} acyl groups, more preferably -C(=O)Me.

The preferred location for a substituent on the C_6 aryl group not bound to Y is para to the bond between the two C6 aryl groups, with the meta position being less preferred. Therefore, if R^3 is 4-phenyl-phenyl, the substituent is preferably at the 4'-position.

In some embodiments of the present invention A is preferably a single bond, whereas in other embodiments A is preferably a C_{1-3} alkylene group. In particular, when R^5 is carboxy, A is more preferably a C_{1-3} alkylene group, with vinylene being most preferred.

R^5 is preferably either:

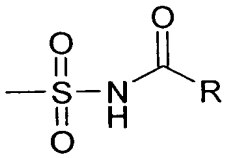
(i) a group of formula (**II**):



(**II**)

; or

(ii) a group of formula (**III**):



(**III**)

with a group of formula (**III**) being more preferred.

Where R^5 is of formula (**II**) of (**III**), R is preferably selected from an optionally substituted C_{5-20} aryl group, and an optionally substituted C_{5-20} aryl-C_{1-7} alkyl group, wherein the C_{1-7} alkyl group is more preferably methyl. In these groups the C_{5-20} aryl group is preferably a heteroaryl group, itself preferably having a single aromatic ring. Such groups may preferably be substituted with C_{1-4} alkyl groups, such as methyl and hydroxy. Thus, preferred R groups include, but are not limited to: phenyl; benzyl; 3,5, dimethyl-isoxazol-4-yl; thiophen-2-yl; 5-methyl-pyridin-yl; and 4-hydroxy-phenyl.

If R in formula (**II**) or (**III**) is a C_{1-7} alkyl group, it is more preferably a C_{1-4} alkyl group, for example methyl or propyl.

Particularly preferred compounds of the present invention include:

4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**);

N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (**5**);

N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-C-phenyl-methanesulfonamide (**6**);

N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-methanesulfonamide (**7**);

Propane-1-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**8**);

3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**9**);

Thiophene-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**10**);

5-Methyl-pyridyl-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (**11**);

4-Hydroxy-*N*-[4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (**13**);

4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**18**);

N-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (**19**);

4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**21**);

N-[4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (**22**);

4-(4'-Chloro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**27**);

4-(4-Benzo[1,3]dioxol-5-yl-phenoxymethyl)-5-methyl-furan-2-carboxylic acid (**28**);

[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (**31**);

4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (**32**);

N-{3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide (**38**);

N-{3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide (**40**);

3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acrylic acid (**43**);

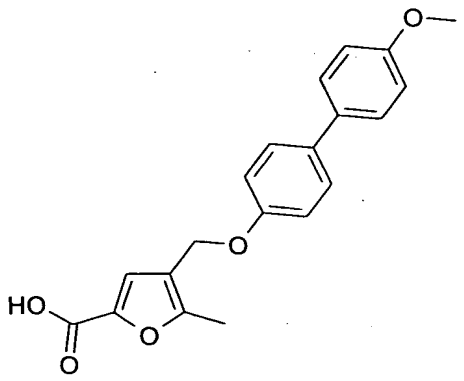
4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (**46**);

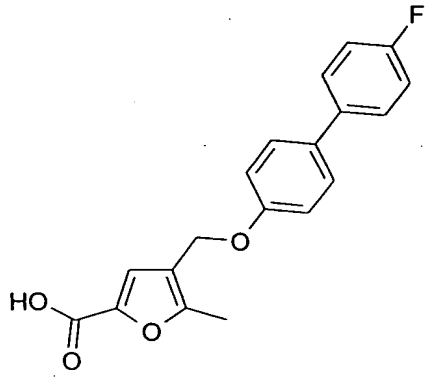
4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (**49**);

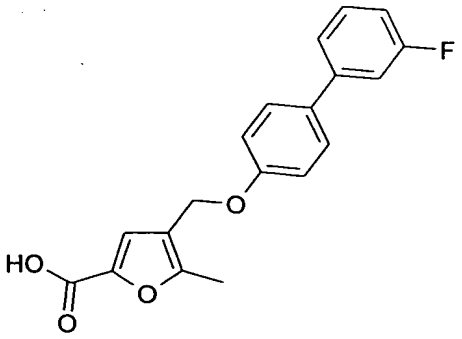
4-(Dibenzofuran-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**50**);

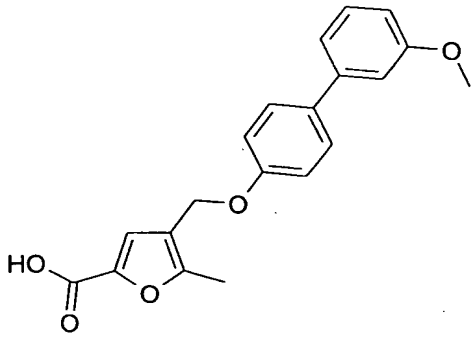
4-[4-(5-Methoxy-pyridin-2-yl)-phenoxymethyl]-5-methyl-furan-2-carboxylic acid (**53**); and
4-[6-(4-Methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-furan-2-carboxylic acid (**56**).

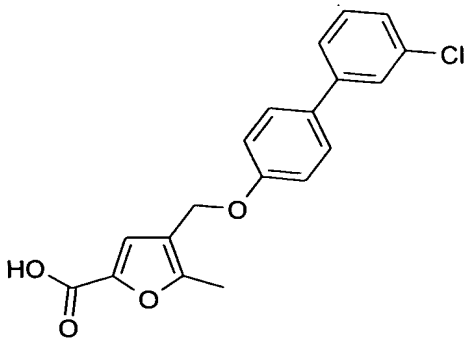
Other embodiments of the present invention include, but are not limited to:

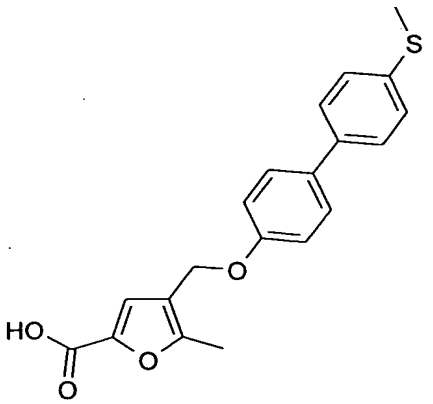


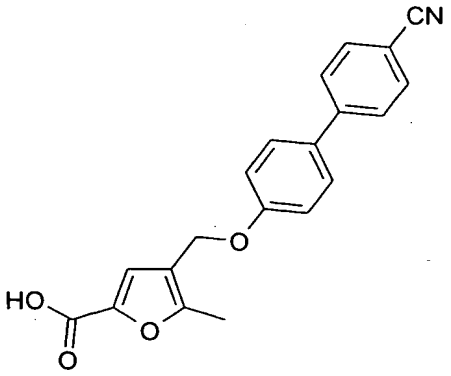


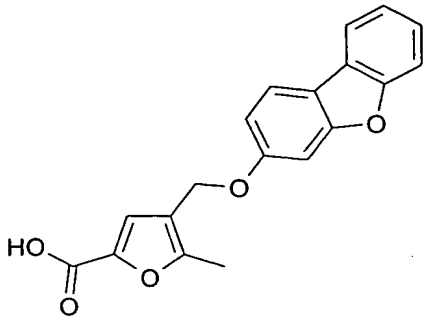


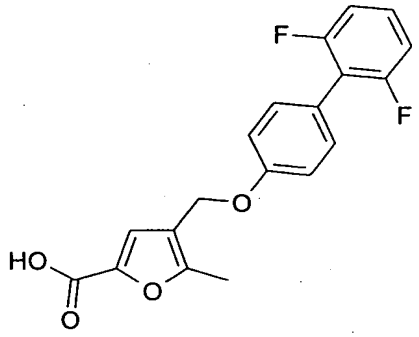


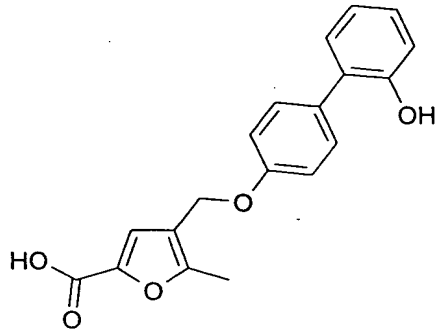


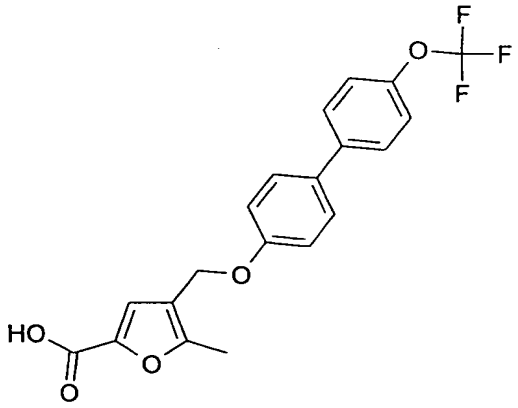


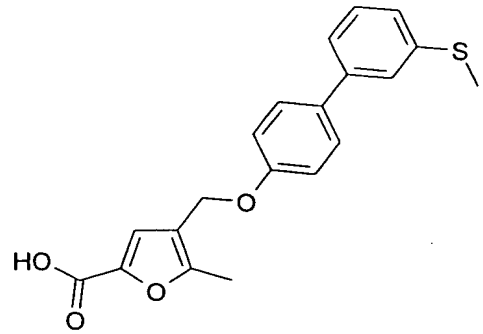

CN
HO
O
O
O

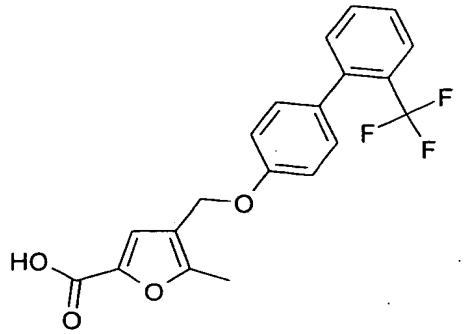

O
O
HO
O
O

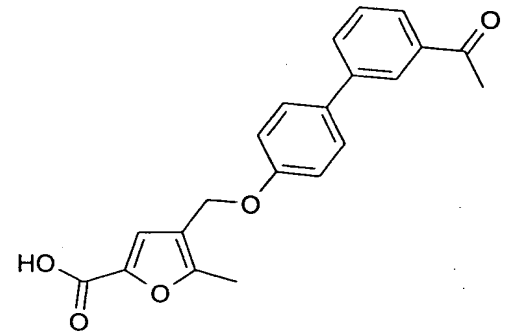

F
F
O
HO
O
O

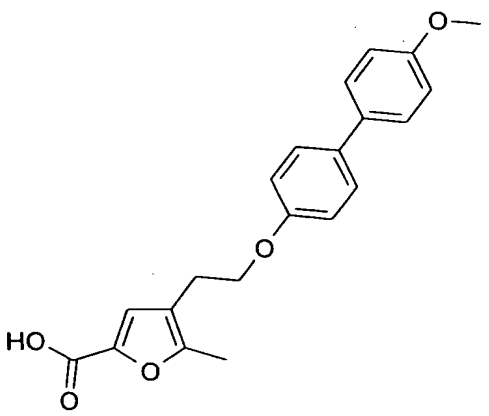

OH
O
HO
O
O

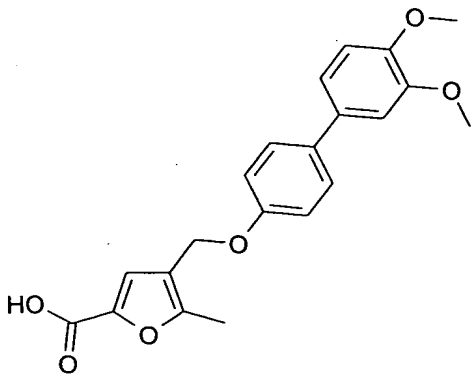

F
O
F
F
O
HO
O
O

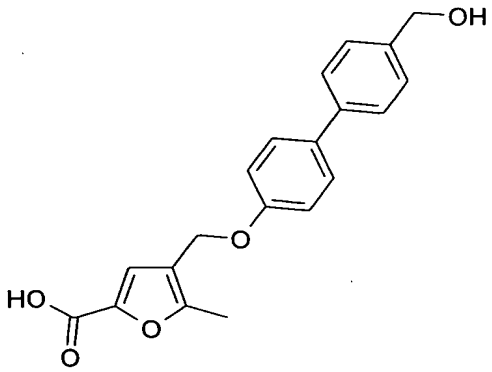

S
O
HO
O
O

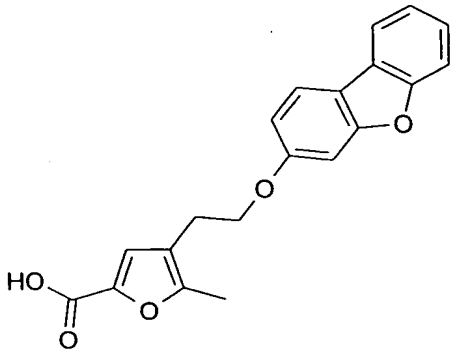

F
F
F
O
HO
O
O

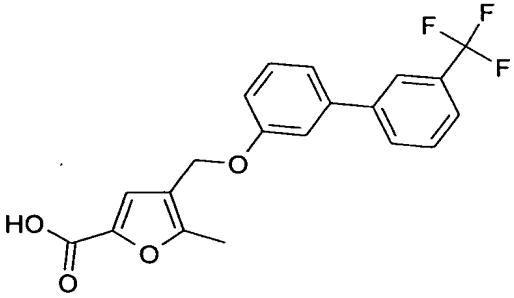

O
O
HO
O
O

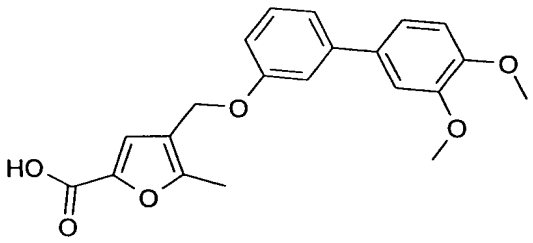


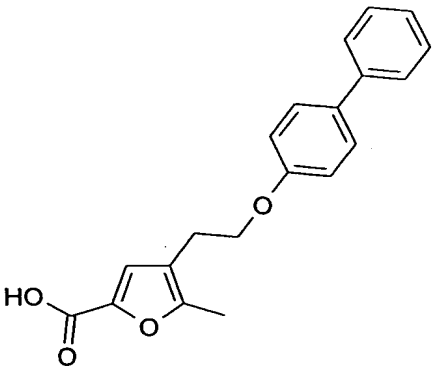


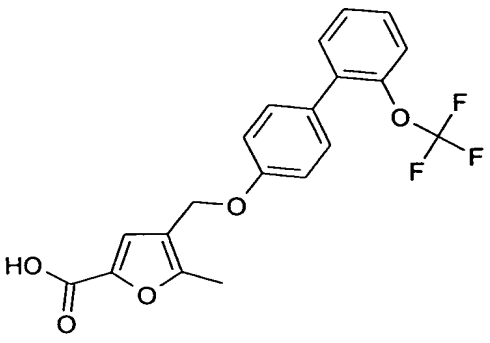


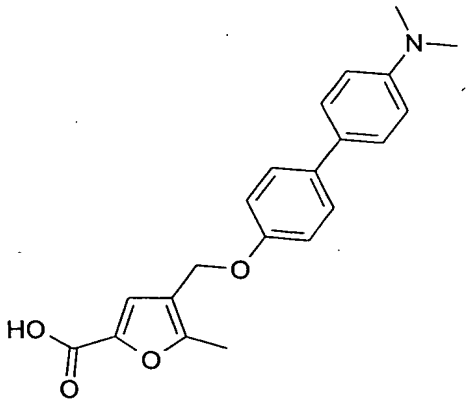


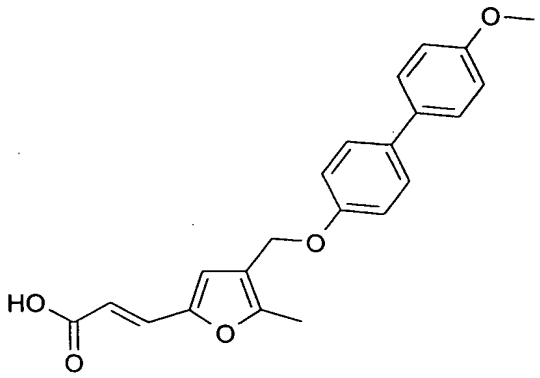


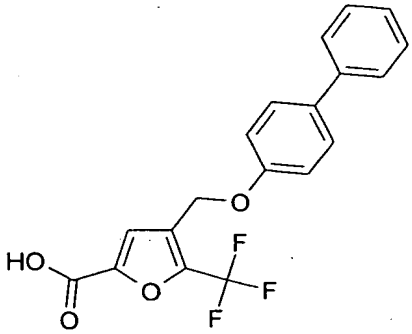


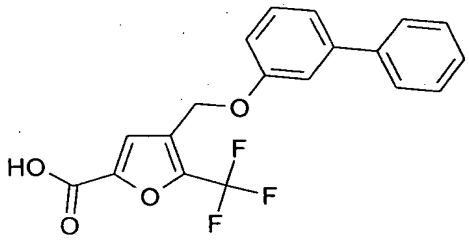


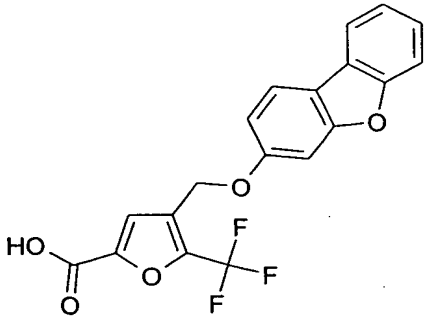


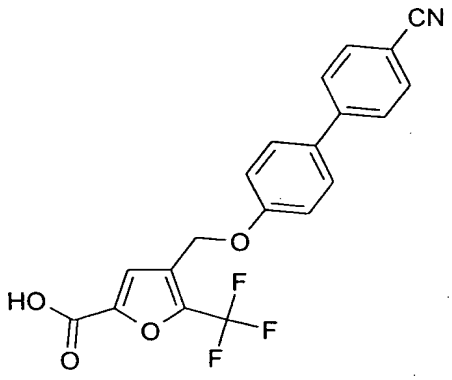


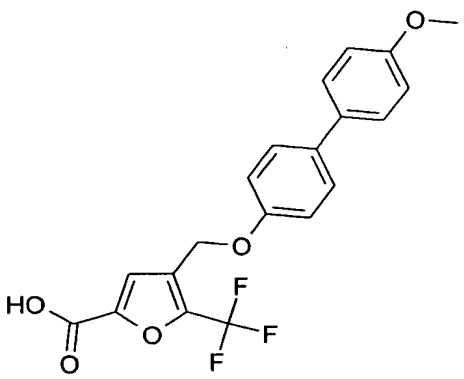


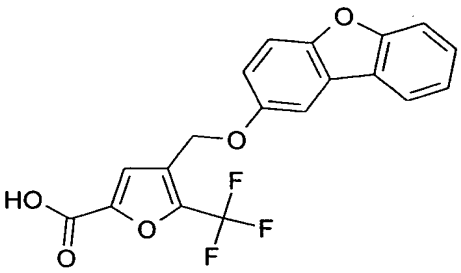


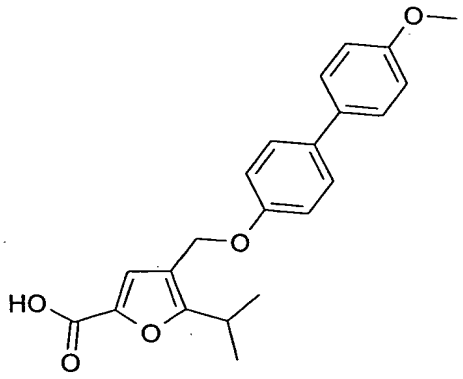


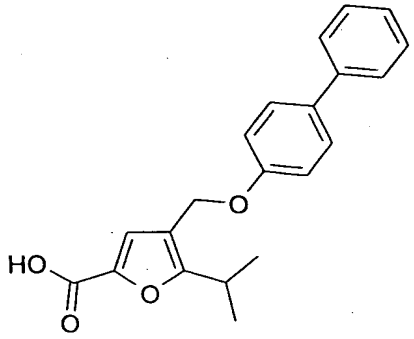


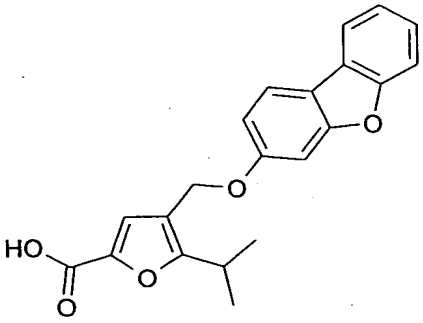


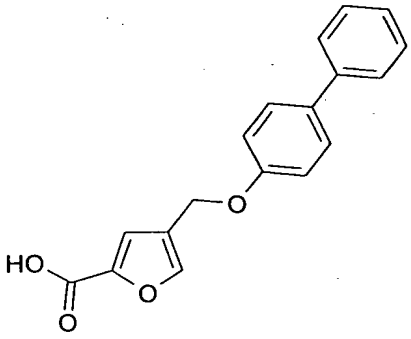


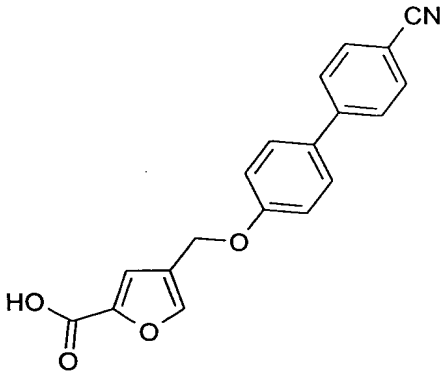


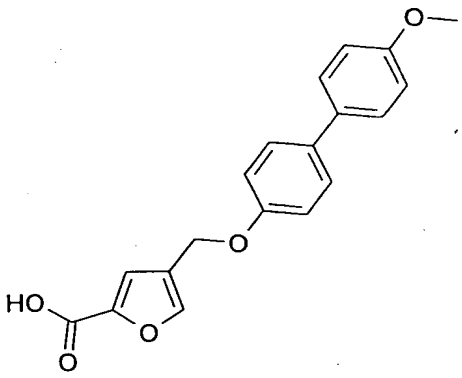












The selectivity of the compound for antagonising EP_4 receptors over the other EP receptors (i.e. EP_1, EP_2, EP_3) can be quantified by dividing the Ki for EP_4 (see below) by the Ki for the other EP receptors (see below). The resulting ratio is preferably 10 or more, more preferably 100 or more.

Synthesis Examples

General Experimental Details

All reactions were carried out under an inert atmosphere of nitrogen.

Where products were purified by flash chromatography the stationary phase used was silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Fluka silica gel 60). An applied pressure of nitrogen of ~10 psi was used to accelerate column elution. Thin layer chromatography (TLC) was carried out on aluminium foil plates coated with silica gel containing a fluorescent indicator (254 nm) (e.g. Fluka 60778).

Petroleum ether refers to that fraction with a boiling point of 40-60°C.

Organic solutions were dried over magnesium sulphate unless otherwise specified.

PS-TsCl refers to Polystyrene scavenger resin (loading 1.97 mmol/g) - Argonaut Technologies (P/N 800277)

Preparative HPLC System

Preparative HPLC was carried out on a C18-reverse-phase column (10 x 2.1 cm i.d Genesis column with 7 µm particle size), eluting with a gradient of acetonitrile (containing 0.1% trifluoroacetic acid) in water (containing 0.1% trifluoroacetic acid) at a flow rate of 5 ml/min. The gradient was started at 50% acetonitrile, and was increased at a rate of 1% per minute up to 90% acetonitrile/water unless otherwise stated. UV detection at 230 nm was used unless otherwise stated.

LC/MS Systems

The Liquid Chromatography Mass Spectroscopy (LC/MS) systems used are as follows.

LC/MS System A:

Mass Spectrometer - Platform LC with electrospray source operating in positive and negative Ion mode. HP1100 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1100 DAD detection and SEDEX ELS detection.

Mobile Phase

A) Water 0.1 % Formic Acid

B) acetonitrile 0.1% Formic Acid

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.50	2.0	5	95
5.00	2.0	5	95
5.50	2.0	95	5

Column - Luna 3u C18(2) 30x4.6mm

LC/MS System B:

Mass Spectrometer - Platform II with electrospray source operating in negative ion mode. HP1100 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1100 DAD detection and SEDEX ELS detection.

Mobile Phase

A) Water 0.1 % Diethylamine

B) acetonitrile

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.00	2.0	5	95
4.50	2.0	5	95
5.00	2.0	95	5
20.00	2.0	95	5

Column - XTerra MS C18 3.5µm 4.6 x 30mm

LCMS System C:

Mass Spectrometer - Finnigan TSQ700 with electrospray source operating in negative ion mode.
HP1050 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1050 Single wavelength UV detector at 254 nm.

Mobile Phase

A) Water 0.1 % Diethylamine

B) acetonitrile

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
1.00	2.0	95	5
15.00	2.0	5	95
17.00	2.0	5	95

18.00	2.0	95	5
20.00	2.0	95	5

Column - XTerra MS C18 3.5µm 4.6 x 30mm

LC/MS System D:

Mass Spectrometer - Finnigan TSQ700 with electrospray source operating in positive or negative ion mode. HP1050 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1050 Single Wavelength UV detector at 254 nm.

Mobile Phase

A) Water 0.1 % formic Acid

B) acetonitrile 0.1% formic Acid

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
1.00	2.0	95	5
15.00	2.0	5	95
17.00	2.0	5	95
18.00	2.0	95	5
20.00	2.0	95	5

Column - Higgins Clipius C18 5µm 100 x 3.0mm

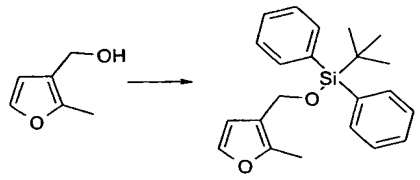
^{1}H NMR system

The ^{1}H NMR spectra were recorded on a Varian Unity Inova 400, which operates at 400 MHz for ^{1}H. It is equipped with a 5mm inverse detection triple resonance probe for detection of ^{1}H. The magnetic field is provided by a 9.4 Tesla Oxford instruments super-conducting magnet. The host computer is a

Sun Microsystems SunBlade 1000 workstation. D_6-dimethylsulphoxide was used as solvent unless stated otherwise. Tetramethylsilane was used as internal standard. Coupling constants are reported in Hz.

Example 1: Synthesis of 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (4) and 4-(Dibenzofuran-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid (50)

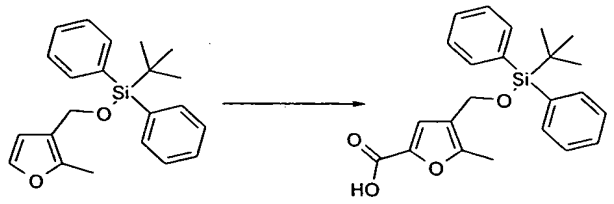
(a) 3-(tert-Butyl-diphenyl-silanyloxymethyl)-2-methyl-furan (2)



1 2

A stirred solution of (2-methyl-3-furan-3-yl)-methanol (**1**)(31.87 g) in N,N-dimethylformamide (250 mL) was treated simultaneously with t-butyldiphenylsilyl chloride (94 g) and imidazole (24 g) and stirring continued for 2 hours at room temperature. The reaction mixture was treated with 1.0 M hydrochloric acid (500 mL), and extracted with diethyl ether (3 x 500 mL). The combined organic extracts were washed successively with 1.0 M hydrochloric acid (500 mL), saturated sodium hydrogen carbonate (500 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with mixtures of diethyl ether in hexane (1:9 to 9:1 by volume) to give compound **2** as a clear oil (67.6 g).

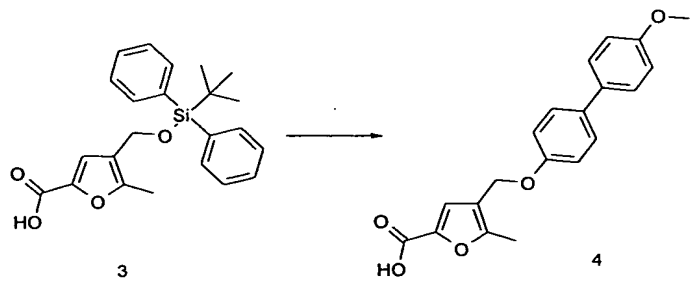
*(b) 4-(tert-Butyl-diphenyl-silanyloxymethyl)-5-methyl-furan-2-carboxylic acid (**3**)*



2 3

A solution of 3-(tert-Butyl-diphenyl-silanyloxymethyl)-2-methyl-furan (**2**) (30.0 g) in tetrahydrofuran (75 mL) was cooled to -78°C with stirring and treated drop-wise with a solution of n-butyllithium (2.5 M in hexanes, 71 mL) over 10 mins. The cooling bath was removed for 0.5 hours and then replaced. A large excess of solid carbon dioxide was added and the mixture allowed to warm to ambient temperature. The reaction mixture was acidified, with 1.0 M hydrochloric acid to pH 2 and extracted into diethyl ether (3 x 500 mL). The combined extracts were washed successively with 1.0 M hydrochloric acid (500 mL), water (500 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with mixtures of diethyl ether in pentane (1:5 to 5:1 by volume) to give compound **3** as a yellow oil (10.36 g). LC/MS System A: R_t = 4.33 mins, m/z (ES^-) = 393 (M^- for $C_{23}H_{26}O_4Si$).

*(c) 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**)*



3 4

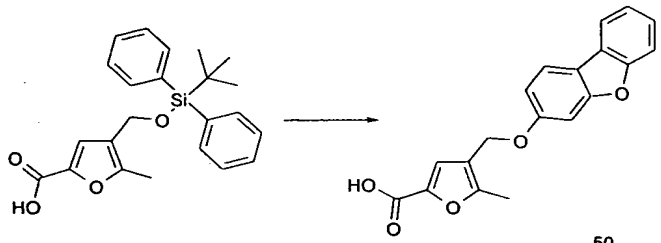
(i) 2-Chlorotrityl chloride resin (1g of nominal loading 1.3 mmol/g) was swelled with dichloromethane (20 mL). After draining, a solution of 4-(tert-butyl-diphenyl-silanyloxymethyl)-5-methyl-furan-2-carboxylic acid (**3**) (0.512 g) and diisopropylethylamine (0.91 mL) in dichloromethane (10 mL) was added and the mixture was shaken at ambient temperature for 16 hours. The resin was drained, washed sequentially with dichloromethane/triethylamine/methanol (20:1:3 by volume) (3 x 25 mL), dichloromethane (3 x 25 mL), N,N-dimethylformamide (2 x 25 mL), dichloromethane (6 x 25 mL), and diethyl ether (2 x 25 mL) and then dried at 40°C *in vacuo*.

(ii) The loaded resin from (i) (2.47 g) was swelled in tetrahydrofuran (15 mL), then treated tetrabutylammonium fluoride (12.8 mL of a 1 M solution in tetrahydrofuran) and shaken at room temperature for 16 hours. The resin was drained, washed sequentially with tetrahydrofuran/water (1:1 by volume), tetrahydrofuran, N,N-dimethylformamide, dichloromethane, diethyl ether, and then dried at 40°C *in vacuo*.

(iii) The loaded resin (2.83g) from (ii) was swelled in tetrahydrofuran (15 mL), and then treated with a solution of 4-hydroxy-4'-methoxydiphenyl (2.93 g) and triphenylphosphine (3.48 g) in tetrahydrofuran (20 mL), followed by the addition of diisopropylazodicarboxylate (2.96 g). The mixture was shaken at room temperature for 16 hours. The resin was drained, washed sequentially with tetrahydrofuran/water (1:1 by volume), tetrahydrofuran, N,N-dimethylformamide, dichloromethane, and then dried at 45°C *in vacuo*. The resin was treated with dichloromethane/trifluoroacetic acid (19:1 by volume) (20 mL) for 20 mins and the solution drained from the resin.

This procedure was repeated. The combined solutions were concentrated in *vacuo* and the residue recrystallised from ethanol to afford compound **4** as a white solid (0.42 g). LC/MS System C: R_t = 4.00 mins, m/z (ES^-) = 337 (M^- for $C_{20}H_{18}O_5$).

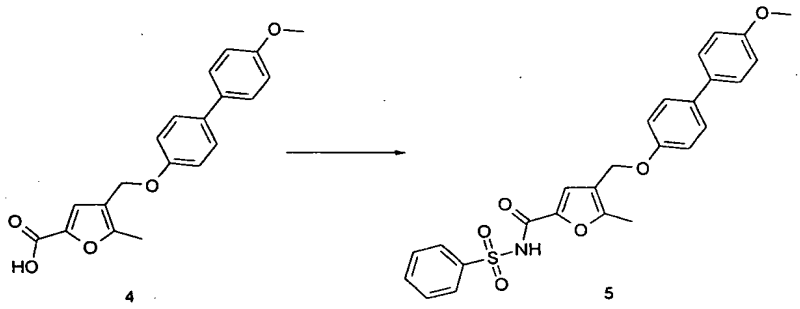
*(d) 4-(Dibenzofuran-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**50**)*



3 50

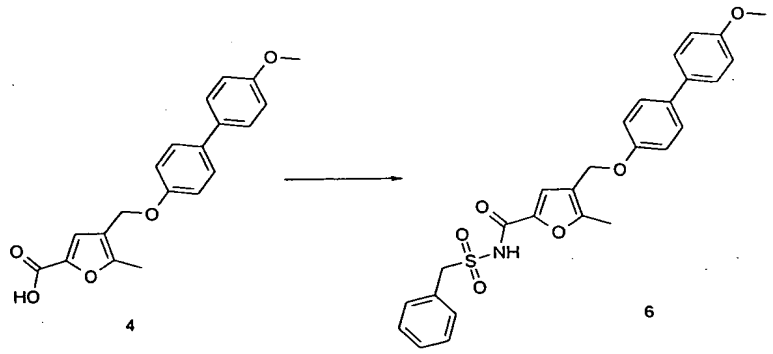
The loaded resin (from example 1(c), (ii)) (100mg) was swelled in tetrahydrofuran, and then treated with a solution of dibenzofuran-3-ol (48mg), triphenylphosphine (68.2mg) and di-isopropyldiazodicarboxylate (52.6mg) in tetrahydrofuran (2mL). The mixture was shaken at room temperature for 72h. The resin was drained, washed sequentially with tetrahydrofuran/water (1:1 by volume), tetrahydrofuran, N,N-dimethylformamide, dichloromethane, and then dried at 45°C *in vacuo*. The resin was treated with dichloromethane/trifluoroacetic acid (19:1 by volume) (2 mL) for 20 mins and the solution drained from the resin. This procedure was repeated. The combined solutions were concentrated in *vacuo;* the residue was triturated with ethyl acetate and dried to furnish compound **50** as a solid. LC/MS System B: R_t = 1.79mins, m/z (ES^-) = 321 ((M-H) for $C_{19}H_{14}O_5$).

Example 2A: Synthesis of *N*-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (5)



A stirred solution of 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (250 mg) in dichloromethane (50 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (142 mg), 4-(N,N-dimethylamino)pyridine (2 mg) and benzenesulfonamide (232 mg). After 16 hours the reaction mixture was concentrated *in vacuo*, the residue dissolved in ethyl acetate (200 mL) and washed successively with water (20 mL), 1.0 M hydrochloric acid (20 mL), saturated sodium hydrogen carbonate solution (20 mL), brine (20 mL), dried and concentrated *in vacuo*. The crude product was purified by HPLC to afford compound **5** as a white solid (30 mg). LC/MS System D: R_t = 5.45 mins, m/z (ES^-) = 476 (M^- for $C_{26}H_{23}NO_6S$).

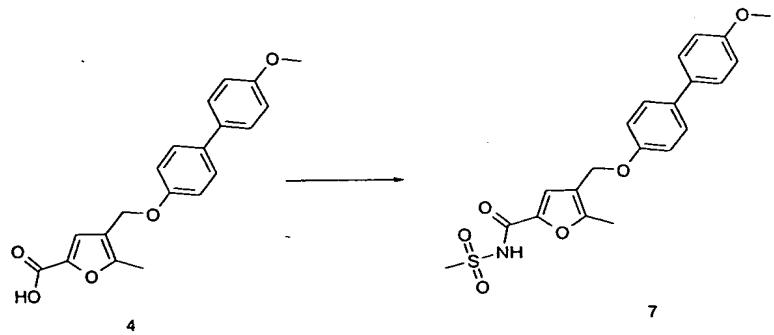
Example 2B: Synthesis of N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-C-phenyl-methanesulfonamide (6)



4 6

N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-C-phenyl-methanesulfonamide was synthesised from 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (30 mg) and phenyl-methanesulfonamide (30.5 mg) in an analogous manner to that described in Example 2A, as a white solid (20 mg). LC/MS System C: R_t = 5.37 mins, m/z (ES^-) = 490 (M^- for $C_{27}H_{25}NO_6S$).

Example 2C: N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-methanesulfonamide (7)

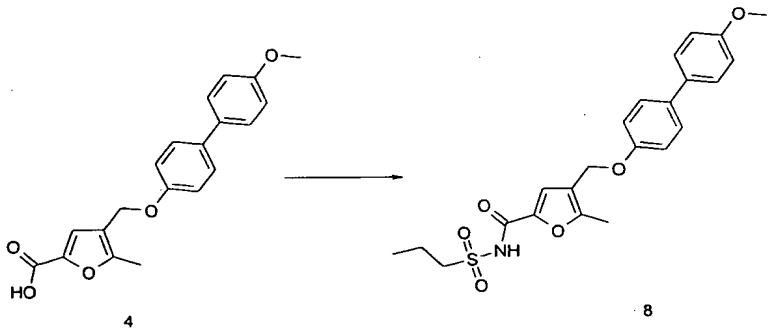


4 7

N-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-methanesulfonamide was synthesised from 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50 mg) and methanesulfonamide (29 mg) in an analogous manner to that described in Example 2A, as a white solid (11.9 mg). LC/MS System C: R_t = 4.50 mins, m/z (ES^-) =

414 (M^- for $C_{21}H_{21}NO_6S$).

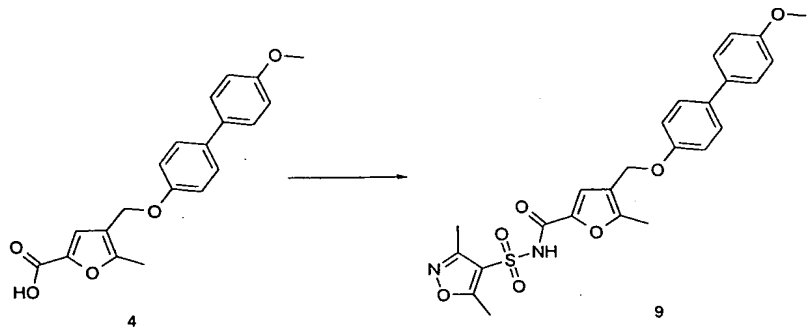
Example 2D: Synthesis of Propane-1-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (8)



4 8

Propane-1-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide was synthesised from 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50 mg) and propane-1-sulfonic amide (36 mg) in an analogous manner to that described in Example 2A, as a white solid (18.2 mg). LC/MS System C: R_t = 4.78 mins, m/z (ES^-) = 442 (M^- for $C_{23}H_{25}NO_6S$).

Example 2E: Synthesis of 3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (9)

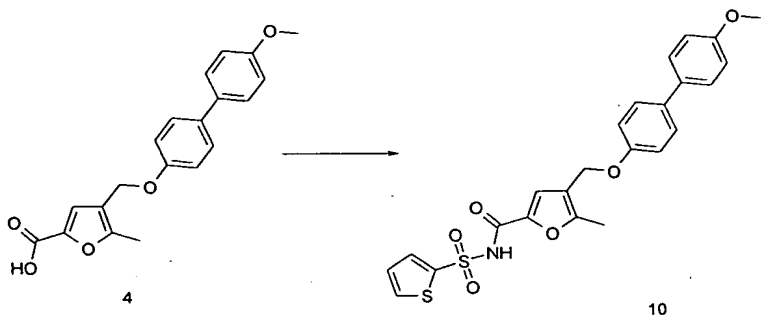


4 9

3,5-Dimethyl-isoxazole-4-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide was synthesised from 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-

methyl-furan-2-carboxylic acid (**4**) (50 mg) and 3,5-dimethylisoxazole-4-sulfonic acid amide (52 mg) in an analogous manner to that described in Example 2A, as a white solid (17.4 mg). LC/MS System C: R_t = 4.91 mins, m/z (ES^-) = 495 (M^- for $C_{25}H_{24}N_2O_7S$).

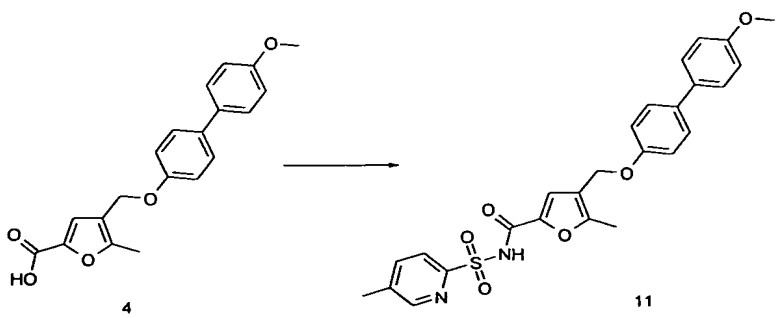
Example 2F: Synthesis of Thiophene-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (10)



4 10

Thiophene-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide was synthesised from 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50 mg) and 2-thiophenesulfonamide (48 mg) in an analogous manner to that described in Example 2A, as a white solid (9.1 mg). LC/MS System C: R_t = 4.94 mins, m/z (ES^-)= 482 (M^- for $C_{24}H_{21}NO_6S_2$).

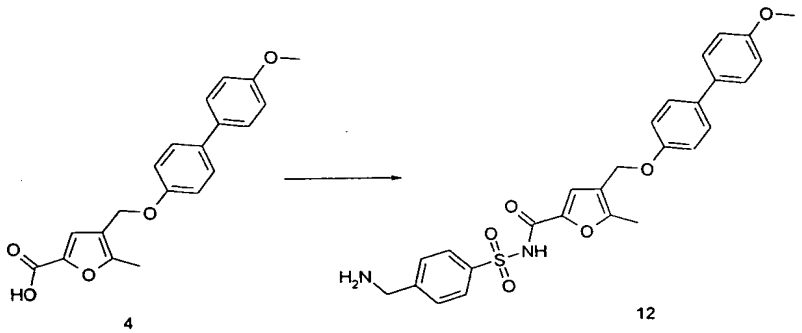
Example 2G: Synthesis of 5-Methyl-pyridyl-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide (11)



4 11

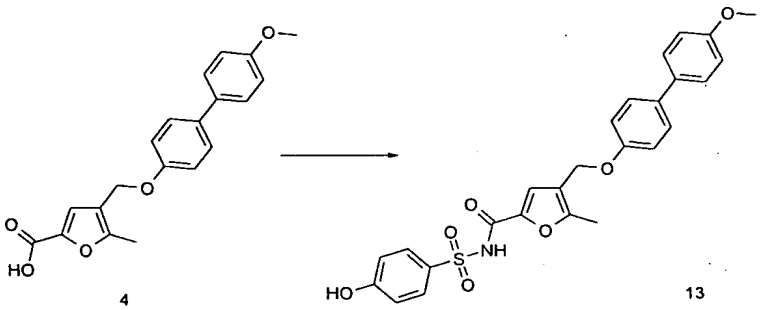
5-Methyl-pyridyl-2-sulfonic acid [4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-amide was synthesised from 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50 mg) and 5-methyl-pyridine-2-sulfonic acid amide (51 mg) in an analogous manner to that described in Example 2A, as a white solid (25 mg). LC/MS System D: R_t = 10.09 mins, m/z (ES^+) = 493 (MH^+ for $C_{26}H_{24}NO_6S$).

Example 2H: Synthesis of 4-Aminomethyl-*N*-[4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide trifluoroacetate (12)



4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50 mg) was reacted with (4-sulphamoyl-benzyl)-carbamic acid tert-butyl ester (85mg) in an analogous manner to that described in Example 2A. The intermediate tert-butyl carbamate was hydrolysed with 1% trifluoroacetic acid/dichloromethane over 24 hours, then concentrated *in vacuo* to give compound **12** as a white solid (10 mg). LC/MS System C: R_t = 4.67 mins, m/z (ES^-) = 493 (M^- 1 for $C_{27}H_{26}N_2O_6S$).

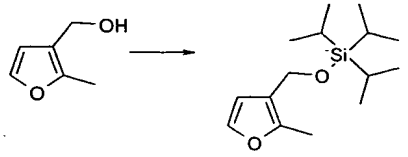
Example 2I: Synthesis of 4-Hydroxy-*N*-[4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (13)



4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**4**) (50 mg) was reacted with acetic acid 4-sulphamoyl-phenyl ester (64 mg) in an analogous manner to that described in Example 2A. The acetic ester intermediate was hydrolysed with sodium methoxide (80 mg) in a mixture of methanol (10mL) and water (1mL) for 1 hour. The solution was concentrated *in vacuo* then partitioned between dichloromethane (10 mL) and water (10 mL). The organic layer was washed with brine (10 mL), dried, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (starting at 30% acetonitrile and increasing at a rate of 1% per minute up to 98% acetonitrile) to give compound **13** as a white solid (15 mg). LC/MS System C: R_t = 3.50 mins, m/z (ES$^-$) = 492 (M^- for $C_{26}H_{23}N_2O_7S$).

Example 3: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (18)

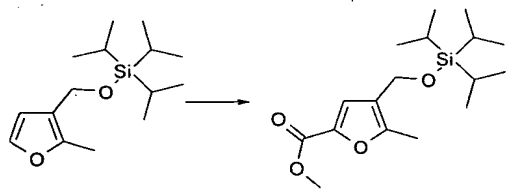
*(a) Triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane (**14**)*



1 14

Triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane was prepared from (2-methyl-furan-3-yl)-methanol (**1**)(24.22 g) in an analogous manner to that described in Example 1 to give compound **14** as a clear oil (54.0 g).

*(b) 5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-carboxylic acid methyl ester (**15**)*

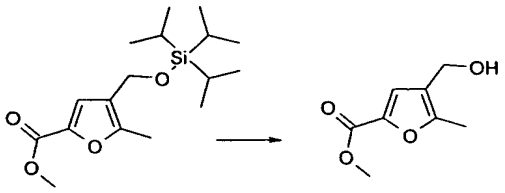


14 15

A solution of triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane (**14**) (10.0 g) in tetrahydrofuran (300 mL) was cooled to -78°C with stirring was treated drop-wise with *sec*-butyllithium (3.0 M in cyclohexane, 37 mL). After 1 hour the reaction mixture was treated drop-wise with a solution of methyl chloroformate (5.2 g) in tetrahydrofuran (30 mL) over 10 mins and stirring was continued at -78°C for 1 hour. The reaction mixture was then treated with saturated ammonium chloride solution (300 mL) and allowed to warm to ambient temperature. The two layers were separated and the organic phase washed with brine (300 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with ethyl acetate/pentane (1:9 by volume) to give

compound **15** as a clear oil.

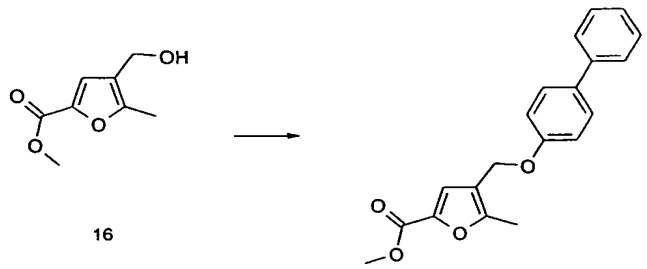
*(c) 4-Hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**)*



15 16

A stirred solution of 5-methyl-4-triisopropylsilanyloxymethyl-furan-2-carboxylic acid methyl ester (**15**) (5.2 g) in tetrahydrofuran (200 mL) was treated with tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 3.2 mL) and stirring continued for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate (350 mL) and washed with water (150 mL). The aqueous phase was re-extracted with ethyl acetate (2 x 100 mL). The combined extracts were dried, concentrated in *vacuo* and the residue was purified by flash chromatography eluting with ethyl acetate/pentane (1:1 by volume) to give compound **16** as a yellow oil.

*(d) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**17**)*

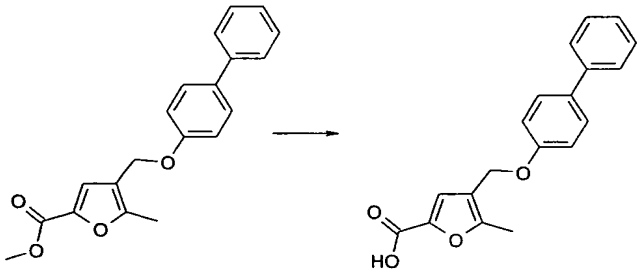


16 17

A solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (1g) in anhydrous tetrahydrofuran

(20mL) was cooled to 0°C under a nitrogen atmosphere. 4-Hydroxybiphenyl (3g) and triphenylphosphine (4.61g) were added and the mixture was treated with di-isopropylazodicarboxylate (3.46mL) dropwise. The mixture was stirred at 0°C for 10min then cooling was removed and the mixture stirred for a further 3 hours. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate (50mL) and water (100mL). The organic phase was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with pentane /ethyl acetate 9:1 by volume to give a mixture of the title compound and 4-hydroxybiphenyl (1.8g). This material was purified further by flash chromatography eluting with dichloromethane/methanol 99:1 by volume to give compound **17** as a white solid (200mg). LCMS System A: R_t = 4.2 mins.

*(e) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**18**)*

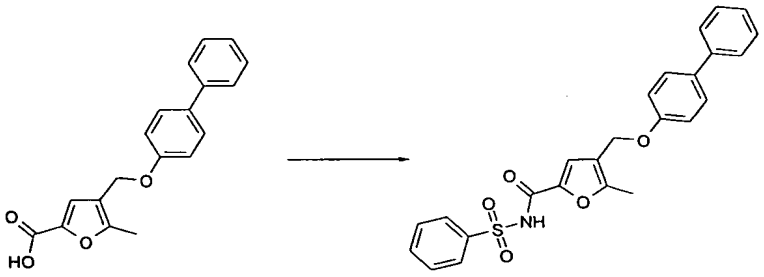


17 18

1M Aqueous lithium hydroxide (18mL) was added to solution of 4-(biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**17**) (1g) in tetrahydrofuran/methanol (2:1 by volume, 100mL) and the mixture stirred at room temperature for 5h. The solvent was removed in vacuo, the residue dissolved in water (20mL) and the solution acidified to pH6 with aqueous dilute hydrochloric acid. The mixture was evaporated to dryness and the residue was purified by HPLC

to afford compound **18** as a white solid (210mg). LC/MS System B: R_t = 4.80 mins, m/z = 307 ((M-1) for $C_{19}H_{16}O_4$).

Example 4: Synthesis of *N*-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (19)

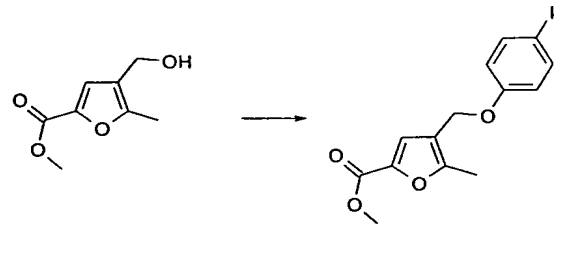


18 19

N-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide was synthesised from 4-(biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**18**) (120 mg) in an analogous manner to that described in Example 2A, as a white solid (20 mg). LC/MS System D: R_t = 9.18mins, m/z (ES^-) = 446 (M^- for $C_{25}H_{21}NO_5S$).

Example 5: Synthesis of 4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (21)

*(a) 4-(4-Iodo-phenoxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**20**)*

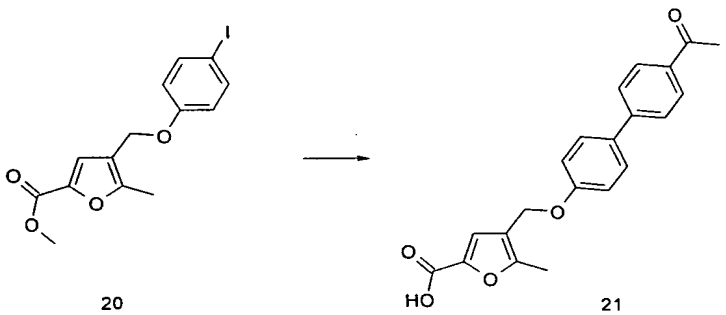


16 20

A solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (1.14 g) in tetrahydrofuran (15 mL) was cooled to 0°C with stirring and treated with 4-

iodophenol (4.6 g), triphenylphosphine (5.5 g) and diisopropylazodicarboxylate (4.2 g). After 10 minutes the cooling bath was removed. After 3 hours the reaction mixture was concentrated *in vacuo* and taken up in ethyl acetate (100 mL) and washed successively with water (100 mL), 1.0 M aqueous sodium hydroxide solution (100 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with ethyl acetate/hexane (1:4 by volume) to give compound **20** as a white solid (1.58 g).

*(b) 4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**21**)*

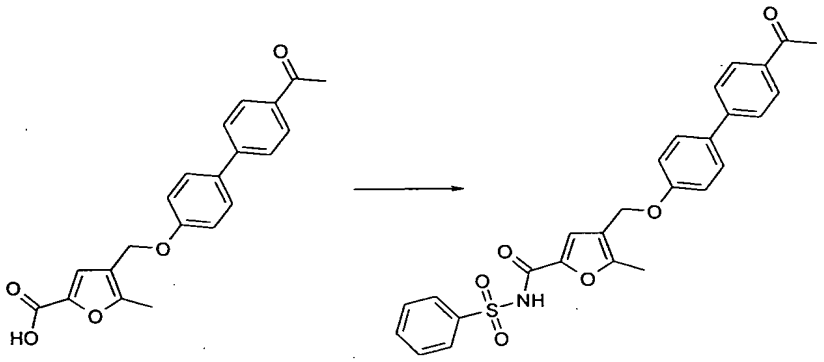


20 21

A stirred mixture of 4-(4-iodo-phenoxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**20**) (0.26 g), 4-acetylphenylboronic acid (0.15 g), N,N-dimethylformamide (30 mL), potassium acetate (0.26 g) and [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (40 mg) was heated at 90°C over night. The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (30 mL) and washed successively with water (30 mL), brine (30 mL), dried and concentrated *in vacuo*. The residue was dissolved in a mixture of tetrahydrofuran/methanol (2:1 by volume) (30 mL) and 1.0 M aqueous lithium hydroxide solution (6.78 mL) and stirred for 16 hours. The reaction mixture was acidified to pH 2 using 0.1 M hydrochloric acid and extracted with ethyl acetate (3 x 25 mL). The extract was dried, concentrated in

vacuo and the residue purified by HPLC to give compound **21** as a white solid (50mg). LC/MS System C: R_t = 4.18 mins, m/z (ES^-) = 349 (M^- for $C_{21}H_{18}O_5$).

Example 6: Synthesis of *N*-[4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide (22)



21 22

N-[4-(4'-Acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carbonyl]-benzenesulfonamide was synthesised from 4-(4'-acetyl-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**21**) (25 mg) in an analogous manner to that described in Example 2A, as a white solid (23 mg). LC/MS System D: R_t = 9.87 mins, m/z (ES^+) = 490 (MH^+ for $C_{27}H_{23}NO_6S$).

Example 7: Synthesis of 4-(4'-Methoxy-biphenyl-4-ylcarbamoyl)-5-methyl-furan-2-carboxylic acid (24)

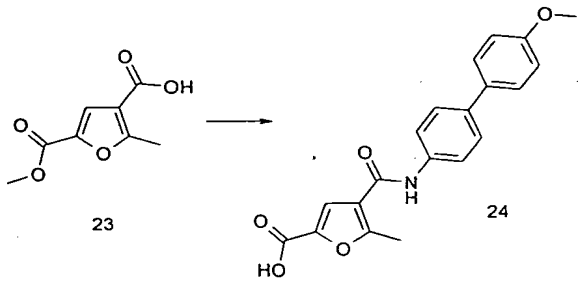
(a) 5-methyl-furan-2,4-dicarboxylic acid-2-methyl ester ***(23)***

16 23

Jones' reagent (Prepared according to Fieser and Fieser, Reagents for Organic Synthesis, Volume 1, page 142, 1967)

was added drop-wise to a stirred solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (100 mg) in acetone (10 mL) until the orange colouration just remained. Stirring was continued for a further 5 hours then the reaction mixture was diluted with diethyl ether (20 mL) and filtered. The filtrate was dried and concentrated *in vacuo* to afford compound **23** as a buff coloured solid.

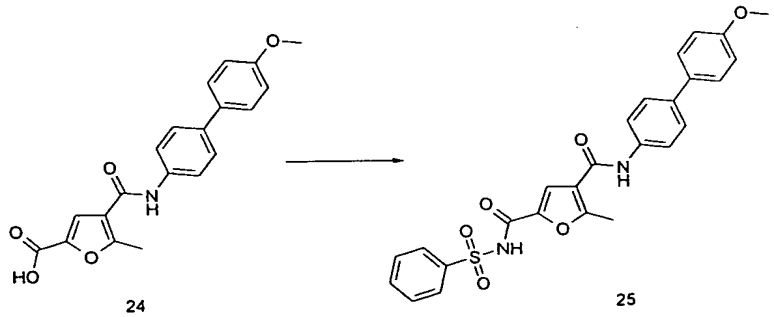
*(b) 4-(4'-Methoxy-biphenyl-4-ylcarbamoyl)-5-methyl-furan-2-carboxylic acid (**24**)*



To a solution of 5-methyl-furan-2,4-dicarboxylic acid-2-methyl ester (**23**) (100 mg) in N,N-dimethylformamide (3.0 mL) was added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (228 mg), diisopropylethylamine (0.56 mL) and 4'-methoxy-biphenyl-4-ylamine (120 mg). The resulting solution was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and washed successively with water (2 x 20 mL), 0.1 M hydrochloric acid (20 mL), water (20 mL), saturated sodium hydrogen carbonate (10 mL) and brine (10 mL). This solution was dried and concentrated *in vacuo*. The residue (170 mg) was dissolved in dichloromethane (5 mL), treated with triethylamine (0.3 mL) and a scavenger resin PS-TsCl (0.6 g) and the mixture shaken for 3 hours at room temperature. The reaction mixture was filtered and concentrated *in-vacuo*. The residue was

dissolved in methanol/tetrahydrofuran (1:3 by volume) (20 mL), treated with 1.0 M aqueous lithium hydroxide solution (2.0 mL) and allowed to stir at room temperature for 4 hours. The pH of the reaction mixture was adjusted to between pH 4 and pH 5 by careful addition of 1.0 M hydrochloric acid (1.0 mL) and partly concentrated *in vacuo*. The residue was then partitioned between ethyl acetate (2 x 25 mL) and water (25 mL) and the combined organic extracts were washed with brine (35 mL), dried (Na_2SO_4), and concentrated *in vacuo* afforded compound **24** as beige solid (58 mg). LC/MS System D: R_t = 7.23 mins, m/z (ES^+) = 351 (MH^+ for $C_{20}H_{17}NO_5$).

Example 8: Synthesis of 5-Benzenesulfonylaminocarbonyl-2-methyl-furan-3-carboxylic acid (4'-methoxy-biphenyl-4-yl)-amide (25)

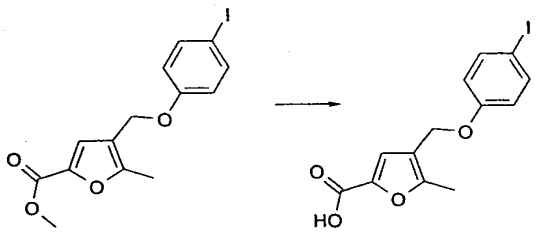


24 25

Compound **25** was synthesised from 4-(4'-Methoxy-biphenyl-4-ylcarbamoyl)-5-methyl-furan-2-carboxylic acid (**24**) (35 mg) in an analogous manner to that described in Example 2A to give the title compound as a white solid (7 mg). LC/MS System A: R_t = 3.86mins, m/z (ES-) = 489 (M-1 for $C_{26}H_{22}N_2O_6S$).

Example 9: Synthesis of 4-(4'-Chloro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (27) and 4-(4-Benzo[1,3]dioxol-5-yl-phenoxymethyl)-5-methyl-furan-2-carboxylic acid (28)

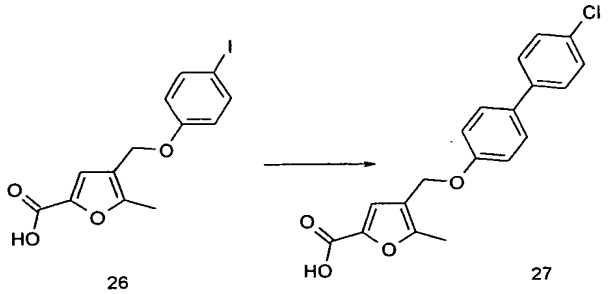
*(a) 4-(4-Iodo-phenoxymethyl)-5-methyl-furan-2-carboxylic acid (**26**)*



20 26

A stirred solution of 4-(4-iodo-phenoxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**20**) (2.7 g) in tetrahydrofuran (25 mL) was treated with a solution of lithium hydroxide (1.5 g) in water (2 mL). After 3 hours the reaction mixture was diluted with water and acidified to pH 2 with 1.0 M hydrochloric acid. The white precipitate was filtered off and dried *in vacuo*. The solid was triturated with ethyl acetate at 0°C then collected by filtration to give compound **26** as a white solid (1.83 g). LC/MS system A: R_t = 1.74 min.

*(b) 4-(4'-Chloro-biphenyl-4-yloxymethyl)-5-methyl-furan-2-carboxylic acid (**27**)*



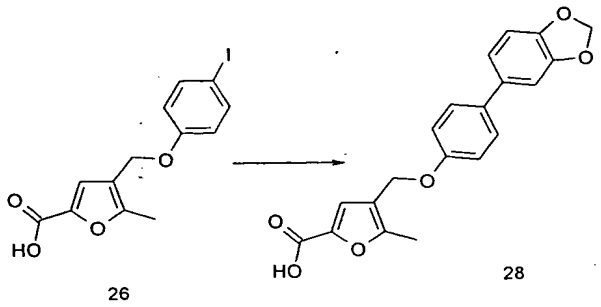
26 27

(i) 2-Chlorotrityl chloride resin (2.55 g of nominal

loading 1.3 mmol/g) was swelled with dichloromethane (20 mL). After draining, a solution of 4-(4-iodo-phenoxymethyl)-5-methyl-furan-2-carboxylic acid (**26**) (1.18 g) and diisopropylethylamine (2.3 mL) in dichloromethane (30 mL) was added and the mixture was shaken at room temperature for 72 hours. The resin was drained, washed sequentially with dichloromethane/triethylamine/methanol (20:1:3 by volume) (3 x 30 mL), dichloromethane (6 x 30 mL), N,N-dimethylformamide (2 x 25 mL), dichloromethane (6 x 25 mL), and diethyl ether (2 x 25 mL) and dried at 40°C *in vacuo*.

(ii) A stirred mixture of the resin from (i) (0.38g), 4-chlorophenylboronic acid (0.30 g), [1,1'-bis-(diphenylphosphino)-ferrocene]-dichloropalladium(II) complex with dichloromethane (1:1) (30 mg), potassium acetate (0.20 g) in N,N-dimethylformamide (15 mL) was heated at 40°C for 48 hours. The resin was darined, then washed sequentially with tetrahydrofuran/water (1:1 by volume), tetrahydrofuran, N,N-dimethylformamide, dichloromethane, diethyl ether and then dried at 45°C *in vacuo*. The resin was treated with dichloromethane/trifluoroacetic acid (19:1 by volume) (20 mL) for 20 mins and the solution drained from the resin. This procedure was repeated. The combined solutions were concentrated *in vacuo* and the residue purified by HPLC to afford compound **27** as a white solid (43 mg). LC/MS System D: R_t = 8.83 mins, m/z (ES^-) = 341 (M^- for $C_{19}H_{15}ClO_4$).

*(c) 4-(4-Benzo[1,3]dioxol-5-yl-phenoxymethyl)-5-methyl-furan-2-carboxylic acid (**28**)*

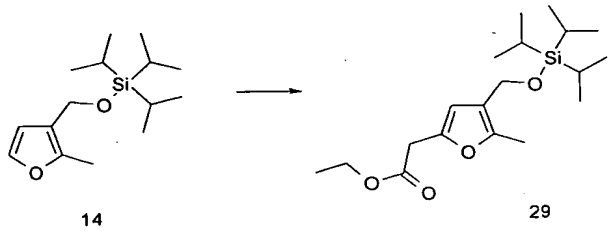


26 28

Compound **28** was synthesised from the resin from (i) in step (b) above and 3,4-methylenedioxyphenyllboronic acid in an analogous manner to that described in step (ii) above. LC/MS System C: R_t = 4.60 mins, m/z (ES^-) = 351 (M^- for $C_{20}H_{16}O_6$).

Example 10: Synthesis of [4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (31) and 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (32)

*(a) (5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-acetic acid ethyl ester (**29**)*

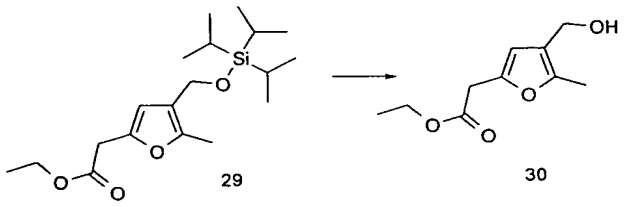


14 29

A solution of triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane (**14**) (5.0 g) in tetrahydrofuran (15 mL) was cooled to -78°C with stirring. This solution was treated drop-wise with n-butyl lithium (2.5 M in hexanes, 8.94 mL). The resulting solution was warmed to 0°C and allowed to stand for 30 minutes after which a solution of dried zinc chloride (3.04 g) in tetrahydrofuran (10 mL) was added and the

resulting solution allowed to stand for a further 1 hour at room temperature. Concurrently, a second reaction vessel was charged with tetrahydrofuran (10 mL), nickel(II) acetylacetonate (120 mg), and triphenylphosphine (122 mg) and cooled (-5°C). Ethyl bromoacetate (1.03 mL) was added to this mixture, followed by the addition of the previously prepared solution of the furyl-zinc chloride. The resulting reaction mixture was allowed to warm to room temperature then stirred for a further 16 hours at room temperature. The reaction was quenched by the addition of saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were successively washed with water (200 mL) and brine (250 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography using a gradient elution (diethyl ether /petroleum ether (40-60°) 1:49 to 1:25 by volume) to give compound 29 as a clear oil (1.44 g). LC/MS System A: R_t = 5.16min.

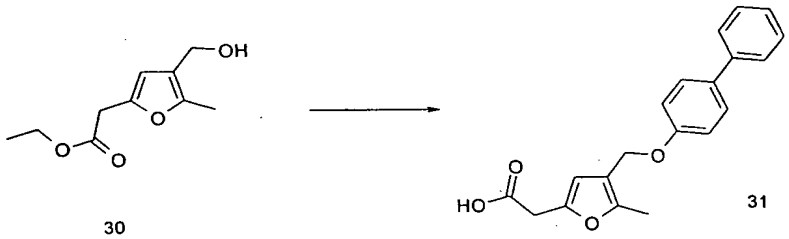
*(b) (4-Hydroxymethyl-5-methyl-furan-2-yl)-acetic acid ethyl ester (**30**)*



A solution of (5-methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-acetic acid ethyl ester (**29**) (0.5 g) in tetrahydrofuran (3.0 mL) was cooled to 0°C with stirring and treated with tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 2.82 mL) under argon. After 30 minutes, the resulting solution was concentrated *in-vacuo* and partitioned between water (30 mL) and ethyl acetate (4 x 25 mL). The combined organic extracts were washed with brine (50 mL),

dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with diethyl ether/petroleum ether (1:1 by volume) to give compound **30** as a clear oil (188 mg). LC/MS System A: R_t = 2.34 mins.

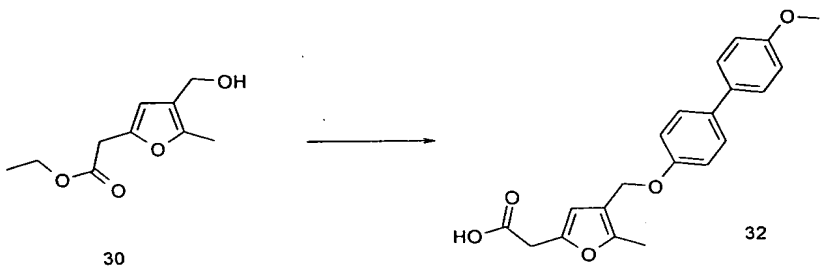
*(c) [4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (**31**)*



A solution of (4-hydroxymethyl-5-methyl-furan-2-yl)-acetic acid ethyl ester (**30**) (199 mg) in tetrahydrofuran (2.5 mL) was cooled to 0°C with stirring. Triphenylphosphine (136.8 mg) and biphenyl-4-ol (95 mg) were added, followed by the drop-wise addition of diisopropylazodicarboxylate (0.15 mL). After stirring for 10 minutes at 0°C the reaction mixture was allowed to warm to room temperature and then stirred for a further 1.5 hours. The reaction mixture was diluted with dichloromethane (5 mL), treated with triethylamine (0.4 mL) and a scavenger resin PS-TsCl (1.0 g) and the mixture was shaken for 3 hours at room temperature. The reaction mixture was filtered and concentrated *in-vacuo*. The residue was purified by flash chromatography using a gradient elution (diethyl ether/petroleum ether (40-60°C) 1:49 to 1:19 by volume). This product (77 mg) was then dissolved in methanol/tetrahydrofuran (2:1 by volume) (3.0 mL), treated with 1.0 M aqueous lithium hydroxide solution (1.5 mL) and allowed to stir at room temperature for 6 hours. The pH of the reaction mixture was adjusted to between pH4 and pH5 by the addition of 1.0 M hydrochloric acid (1.0 mL), treated

with saturated ammonium chloride solution (25 mL) and then extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were further washed with brine (35 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by HPLC (starting at 35% acetonitrile, and increasing at a rate of 1% per minute up to 95% acetonitrile) to give compound **31** as white solid (25 mg). LC/MS System C: R_t = 4.97 mins, m/z (ES^-) = 321 (M^- for $C_{20}H_{18}O_4$).

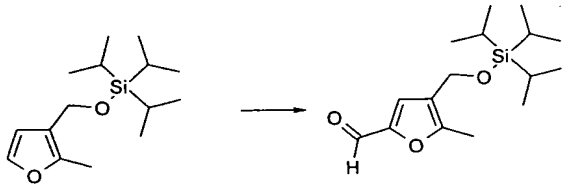
*(d) [4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid (**32**)*



[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acetic acid was prepared from (4-hydroxymethyl-5-methyl-furan-2-yl)-acetic acid ethyl ester (**30**) (94 mg) and 4'methoxy-biphenyl-4-ol in an analogous manner to that described in Example 10(c). The crude product was purified by flash chromatography, eluting with diethyl ether/petroleum ether (40-60°C) (1:1 by volume), to give compound **32** as a beige solid (15 mg). LC/MS System C: R_t = 4.94 mins, m/z (ES^-) = 351 (M^- for $C_{21}H_{20}O_5$).

Example 11: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (37) and *N*-{3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide (38)

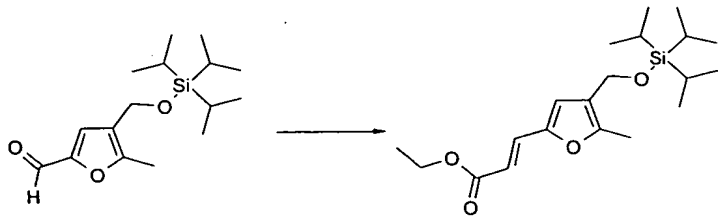
*(a) 5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-carbaldehyde (**33**)*



14 33

A solution of triisopropyl-(2-methyl-furan-3-ylmethoxy)-silane (**14**) (10 g) in tetrahydrofuran (250 mL) was cooled to -78°C with stirring, and then sec-butyllithium (1.3 M in cyclohexane; 37.25 mL) was added drop-wise over 10 mins. After stirring for 45 mins at -78°C, the cooling bath was removed for a period of 15 mins then re-introduced. A solution of N,N-dimethylformamide (14.4 mL) in tetrahydrofuran (25 mL) was added drop-wise and the resulting reaction mixture was stirred at -78°C for a further 2 hours. The reaction mixture was allowed to warm to room temperature and then poured into saturated ammonium chloride solution (150 mL). This mixture was extracted with diethyl ether (2 x 350 mL), and the combined organic extracts were washed with water (500 mL) and brine (500 mL), dried, and concentrated *in vacuo* to give compound **33** as an amber coloured oil. LC/MS System A: R_t = 4.86 mins.

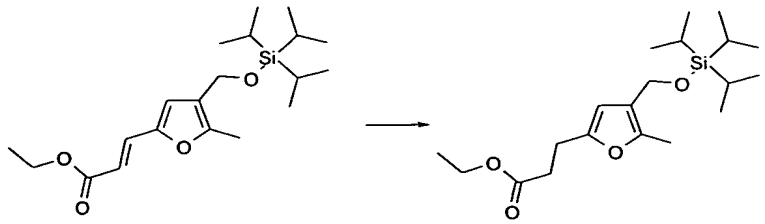
*(b) 3-(5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-acrylic acid ethyl ester (**34**)*



33 34

A stirred solution of 5-methyl-4-triisopropylsilanyloxymethyl-furan-2-carbaldehyde (**33**) (10.6 g) in tetrahydrofuran (25 mL) was treated with triethylphosphonoacatete (7.81 mL) and lithium hydroxide (1.65 g). The resulting mixture was stirred for 16 hours then concentrated *in vacuo* and the residue partitioned between water (100 mL) and diethyl ether (3 x 100 mL). The combined organic extracts were further washed with water (200 mL) and brine (200 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with diethyl ether/petroleum ether (1:40 by volume) to give compound **34** as a clear yellow oil (10.56 g). LC/MS System A: R_t = 4.59 mins.

*(c) 3-(5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-propionic acid ethyl ester (**35**)*

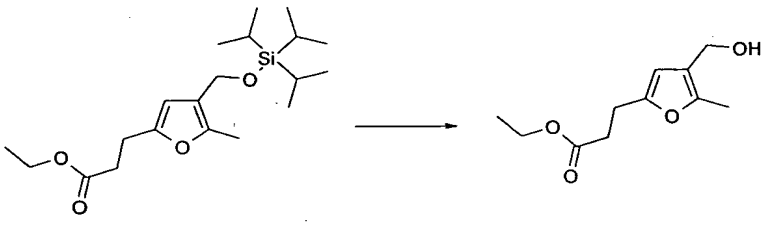


34 35

A solution of 3-(5-methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-acrylic acid ethyl ester (**34**) (1.0 g) in ethyl acetate (70 mL) was treated with 5% w/w palladium on carbon

(350 mg) and hydrogenated at 1 atmosphere for exactly 1¼ hours at room temperature. The reaction mixture was filtered through filter-aid and then concentrated *in vacuo* to afford compound **35** as a clear oil (1.05 g). LC/MS System A: R_t = 5.52 mins.

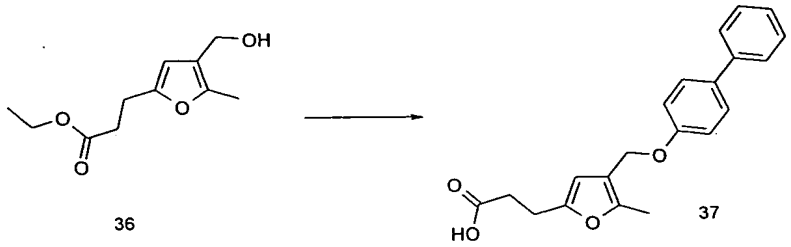
*(d) 3-(4-Hydroxymethyl-5-methyl-furan-2-yl)-propionic acid ethyl ester (**36**)*



35 36

A solution of 3-(5-methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-propionic acid ethyl ester (**35**) (1.05 g) in tetrahydrofuran (8.0 mL) was cooled to 0°C with stirring and was treated with tetrabutylammonium fluoride (5.46 mL of a 1.0 M solution in tetrahydrofuran). After 15 minutes the reaction mixture was concentrated *in vacuo* then partitioned between water (100 mL) and diethyl ether (3 x 50 mL). The combined organic extracts were washed with saturated brine (250 mL), dried (sodium sulphate), and then concentrated *in vacuo*. The residue was purified by flash chromatography eluting with diethyl ether/petroleum ether (1:24 by volume) to give compound **36** as a clear oil (295 mg). LC/MS System A: R_t = 2.68 mins.

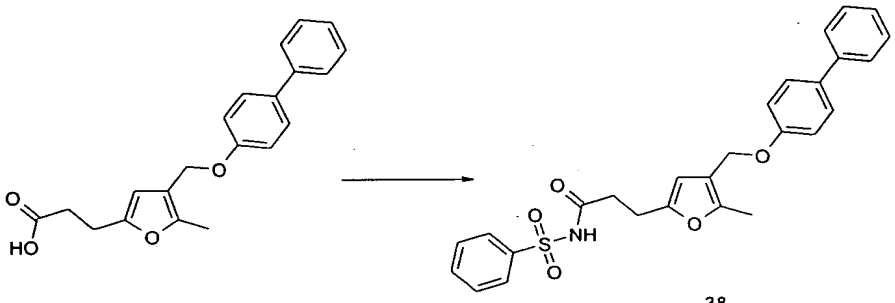
*(e) 3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (**37**)*



To a stirred, cooled 0°C solution, in tetrahydrofuran (2.5 mL), a solution of 3-(4-hydroxymethyl-5-methyl-furan-2-yl)-propionic acid ethyl ester (**36**) (400 mg) in tetrahydrofuran (2.5 mL) was cooled to 0°C and treated successively with triphenylphosphine (542 mg), biphenyl-4-ol (353 mg) and diisopropylazodicarboxylate (0.41 mL). After stirring for 10 mins at 0°C the reaction mixture was allowed to warm to room temperature and then stirred for a further 16 hours. The reaction mixture was concentrated *in-vacuo* then re-dissolved in dichloromethane (15 mL) and treated with triethylamine (1.50 mL) and a scavenger resin PS-TsCl (2.5 g) and the mixture was shaken for 6 hours at room temperature. The reaction mixture was purified by flash chromatography, eluting with a mixture of diethyl ether in petroleum ether (40-60°C) (7:93 by volume). The purified product (320 mg) was dissolved in methanol/tetrahydrofuran (2:1 by volume) (18 mL), treated with 1.0 M aqueous lithium hydroxide solution (9 mL) and allowed to stir at room temperature for 6 hours. The pH of the reaction mixture was adjusted to between pH4 and pH5 by the addition of 1.0 M hydrochloric acid (~ 5.0 mL), then treated with saturated ammonium chloride (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were further washed with brine (35 mL), then dried (sodium sulphate) and concentrated *in vacuo*. A sample of the crude product (50 mg) was purified by HPLC to give compound **37** as white solid (25mg). LC/MS

System C: R_t = 5.33 mins, m/z (ES^-) = 335 (M^- for $C_{21}H_{20}O_4$).

(f) N-{3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide ***(38)***

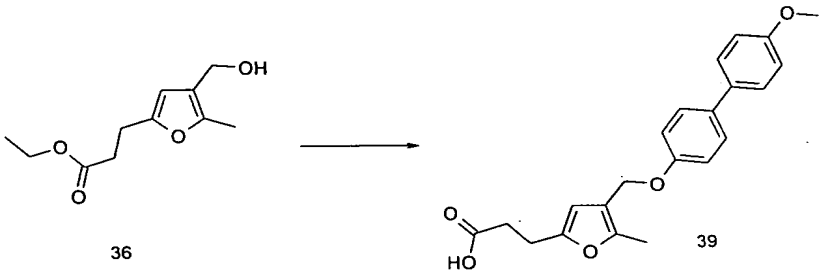


37 38

To a stirred solution of 3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (**37**) (100 mg) in a mixture tetrahydrofuran (20 mL) and N,N-dimethylformamide (5 mL) was added 4-(N,N-dimethylamino)pyridine (2.0 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (70 mg) and benzenesulfonamide (93 mg). After 16 hours at room temperature the reaction mixture was concentrated *in-vacuo*, then partitioned between 1.0 M hydrochloric acid (25 mL) and ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (25 mL), dried, and concentrated *in vacuo*. The crude product was purified by HPLC to give compound **38** (50 mg). LC/MS System C: R_t = 5.82 mins, m/z (ES^-) = 475 (M^- for $C_{27}H_{25}O_5S$).

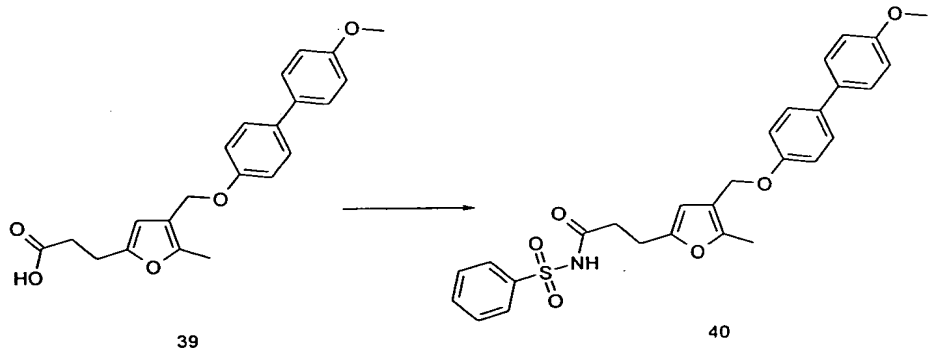
Example 12: Synthesis of 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (39) and *N*-{3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide (40)

*(a) 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (**39**)*



Compound **39** was prepared from 3-(4-hydroxymethyl-5-methyl-furan-2-yl)-propionic acid ethyl ester (**36**) (400 mg) and 4'-methoxy-biphenyl-4-ol (416 mg) in an analogous manner to that described in Example 11(e), as white solid (30 mg). LC/MS System C: R_t = 5.31 mins, m/z (ES^-) = 365 (M^- for $C_{22}H_{22}O_5$).

*(b) N-{3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionyl}-benzene sulfonamide (**40**)*

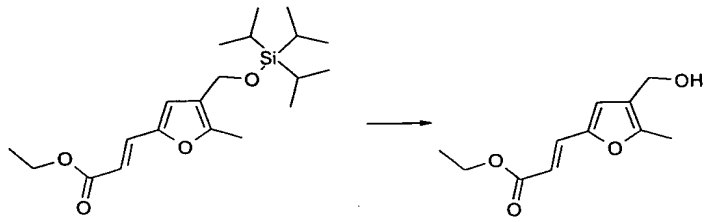


Compound **40** was prepared from 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-propionic acid (**39**) (65 mg) in an analogous manner to that described in Example 11(f). The crude product was purified by HPLC to give the

title compound as white solid (27 mg). LC/MS System C: R_t = 5.78 mins, m/z (ES^-) = 504 (M^- for $C_{28}H_{27}NO_6S$).

Example 13: Synthesis of 3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acrylic acid (42) and 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acrylic acid (43)

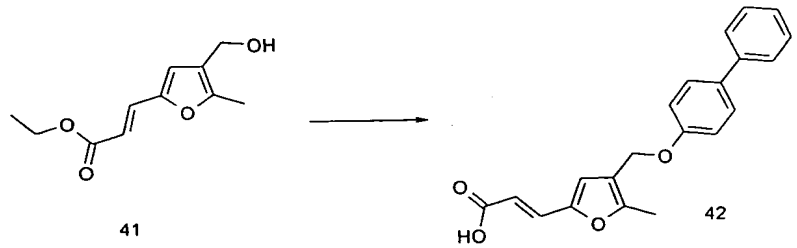
*(a) 3-(4-Hydroxymethyl-5-methyl-furan-2-yl)-acrylic acid ethyl ester (**41**)*



34 41

Compound **41** was prepared from 3-(5-Methyl-4-triisopropylsilanyloxymethyl-furan-2-yl)-acrylic acid ethyl ester (**34**) (10.56 g) in an analogous manner to that described for Example 11(d). The crude product was purified by flash chromatography eluting with diethyl ether/petroleum ether (2:3 by volume) to give compound **41** as a clear yellow oil (4.7 g). LC/MS System A: R_t = 2.82mins.

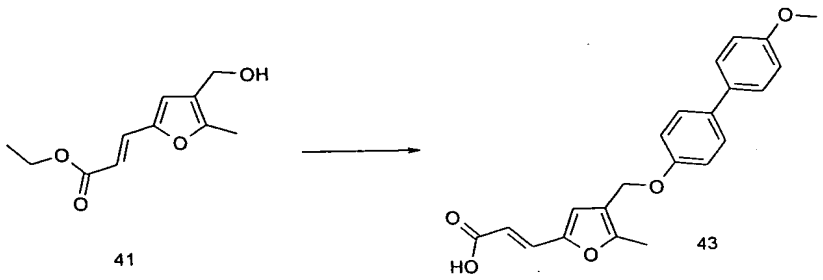
*(b) 3-[4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acrylic acid (**42**)*



Compound **42** was prepared from 3-(4-hydroxymethyl-5-methyl-furan-2-yl)-acrylic acid ethyl ester (**41**) (1.0 g) and

biphenyl-4-ol (811 mg) in an analogous manner to that described in Example 11(e) as a white solid (100 mg). LC/MS System C: R_t = 4.91 mins, m/z (ES^-) = 333 (M^- for $C_{21}H_{18}O_4$).

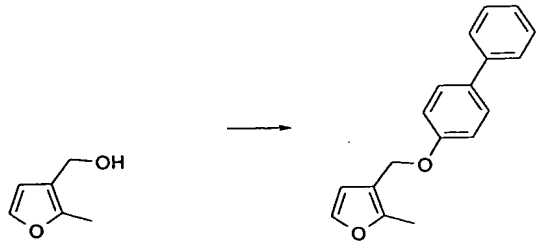
(c) 3-[4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-yl]-acrylic acid ***(43)***



Compound **43** was prepared from 3-(4-hydroxymethyl-5-methyl-furan-2-yl)-acrylic acid ethyl ester (**41**) (1.0 g) and 4'-methoxy-biphenyl-4-ol (956 mg) in an analogous manner to that described in Example 11(e), as a white solid (100 mg). LC/MS System C: R_t = 4.85 mins, m/z (ES^-) = 363 (M^- for $C_{22}H_{20}O_5$).

Example 14: Synthesis of 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (46)

(a) 3-(Biphenyl-4-yloxymethyl)-2-methyl-furan ***(44)***

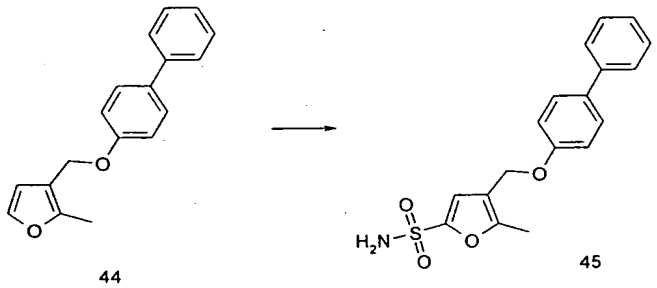


1 44

A solution of (2-methyl-furan-3-yl)-methanol (**1**)(5.0 g) in diethyl ether (75 mL) was cooled to 0°C with stirring and treated with triphenylphosphine (12.85 g) and biphenyl-4-ol (7.59 g). The resulting solution was then treated drop-wise with diisopropylazodicarboxylate (9.75 mL). After stirring

for 10 minutes at 0°C the reaction mixture was allowed to warm to room temperature and then stirred for a further 3 hours. The reaction mixture was then filtered and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with diethyl ether/petroleum ether (1:19 by volume), to give compound **44** as a white solid (7.0 g). LC/MS System A: R_t = 4.38 mins.

*(b) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid amide (**45**)*

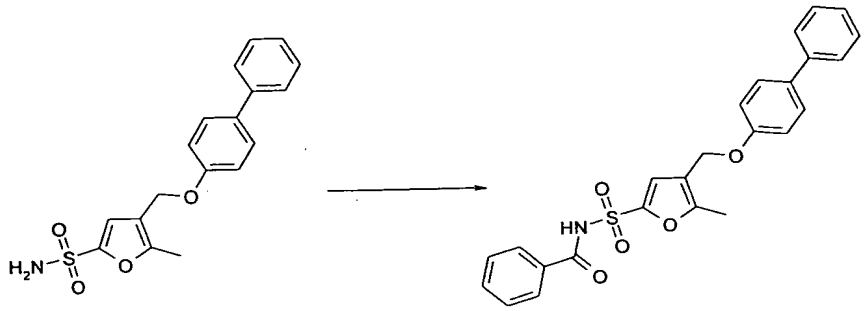


44 45

A solution of 3-(biphenyl-4-yloxymethyl)-2-methyl-furan (**44**) (5g) in tetrahydrofuran (30 mL) was cooled to -78°C with stirring and was treated with butyllithium (2.5 M in hexanes; 9.84 mL) drop-wise over 10 minutes. After stirring for 45 mins at -78°C, cooling was removed for a period of 15 minutes then re-introduced. A stream of sulphur dioxide gas was then passed over the surface of the reaction mixture until the pH of the reaction was between pH6 and pH7. Stirring was continued for a further 1.5 hours at -78°C and then pentane was added (50 mL). The resulting precipitate was collected by filtration and then re-suspended in water (75 mL). This suspension was cooled to 0°C and treated with sodium acetate (3.88 g) and hydroxylamine-O-sulfonic acid (2.67 g) and stirred at room temperature for 16 hours. The reaction mixture was diluted with water (300 mL) and extracted into ethyl acetate (3 x 250 mL). The combined organic extracts were washed successively with saturated

sodium hydrogen carbonate (300 mL) and brine (300 mL), dried, and concentrated *in vacuo*. This material was purified by flash chromatography, eluting with diethyl ether/petroleum ether (2:3 by volume) to give a beige coloured solid (998 mg). A sample of this material (100 mg) was further purified by HPLC to give compound **45** as white solid (55 mg). LC/MS System A: R_t = 3.70 mins.

*(c) 4-(Biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide **(46)***

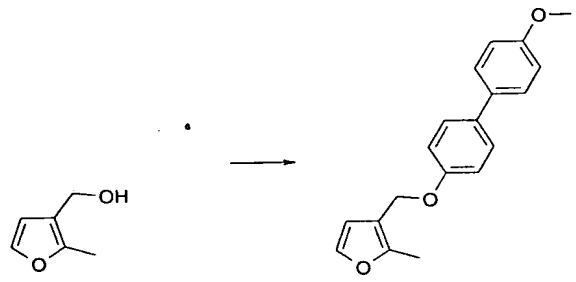


45 46

To a stirred solution of benzoic acid (61 mg) in a mixture of tetrahydrofuran (10 mL) and N,N-dimethylformamide (5 mL) was added 4-(N,N-dimethylamino)pyridine (3.0 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (118 mg) and 4-(biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid amide (**45**) (206 mg). After 16 hours at room temperature the reaction mixture was concentrated *in-vacuo*, then partitioned between 0.1 M hydrochloric acid (30 mL) and ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by HPLC to give compound **46** as light beige solid (17 mg). LC/MS System C: R_t = 5.69 mins, m/z (ES^-) = 446 (M^- for $C_{25}H_{21}NO_5S$).

Example 15: Synthesis of 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (49)

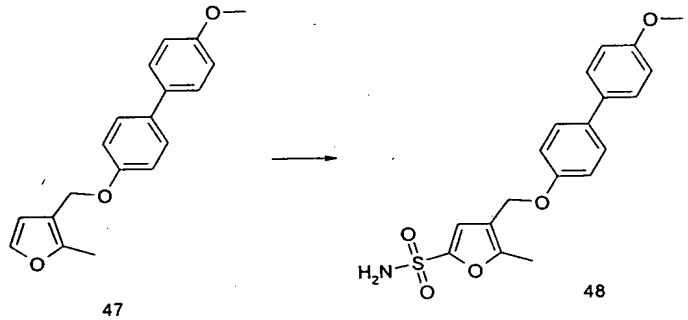
(a) 3-(4'-Methoxy-biphenyl-4-yloxymethyl)-2-methyl-furan (47)



1 47

Compound **47** was prepared from (2-methyl-furan-3-yl)-methanol (**1**) (3.0 g) and 4'-methoxy-biphenyl-4-ol (5.38g) in an analogous manner to that described in Example 14(a). LC/MS System A: R_t = 4.58 mins.

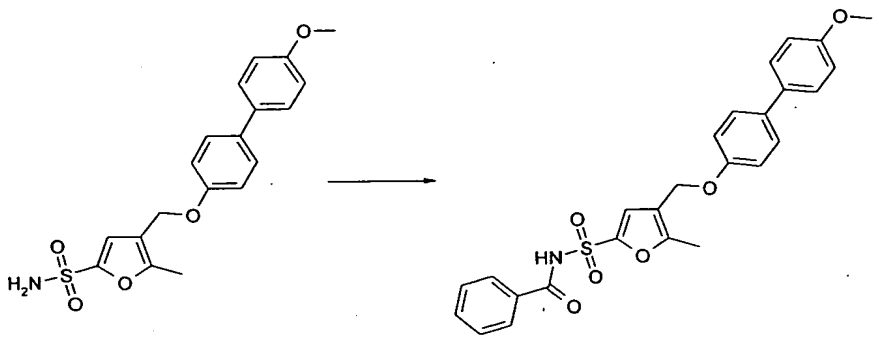
(b) 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid amide (48)



47 48

Compound **48** was prepared from 3-(4'-methoxy-biphenyl-4-yloxymethyl)-2-methyl-furan (**47**) (1.2 g) in a manner analogous to that described in Example 14(b). LC/MS System A: R_t = 3.63 mins.

*(c) 4-(4'-Methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid benzoylamide (**49**)*

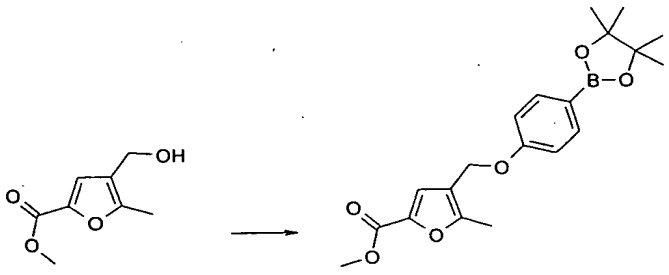


48 49

To a stirred solution of 4-(4'-methoxy-biphenyl-4-yloxymethyl)-5-methyl-furan-2-sulfonic acid amide (**48**) (25 mg) and triethylamine (11.5 µL) in dichloromethane (2.5 mL) was added a solution of benzoyl chloride (10 µL) in dichloromethane (1.0 mL). The resulting solution was stirred at room temperature under argon for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue purified by HPLC to give compound **49** as white beige solid (23 mg). LC/MS System C: R_t = 5.37 mins, m/z (ES^-) = 476 (M^- for $C_{26}H_{23}NO_6S$).

Example 16: Synthesis of 4-[4-(5-Methoxy-pyridin-2-yl)-phenoxymethyl]-5-methyl-furan-2-carboxylic acid (53)

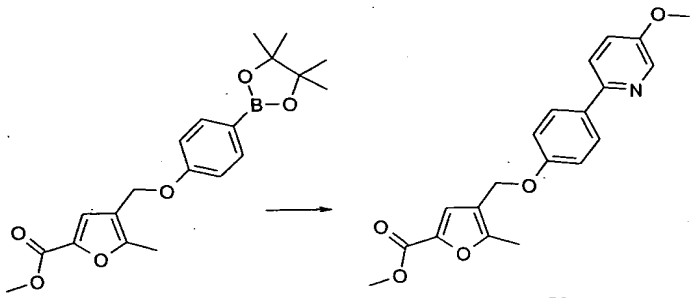
(a) 5-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxymethyl]-furan-2-carboxylic acid methyl ester ***(51)***



16 51

A mixture of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (0.5g), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (1.9g) and triphenylphosphine (2.3g) in dry tetrahydrofuan (20mL) under a nitrogen atmosphere was cooled to 0°C. Di-isopropylazodicarboxylate (1.8mL) was added drop-wise and the mixture was stirred at room temperature for 72 hours. After concentrating *in vacuo*, the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was extracted with pentane and the pentane phase was decanted and concentrated to give compound **51** as an oil. This was used without further purification.

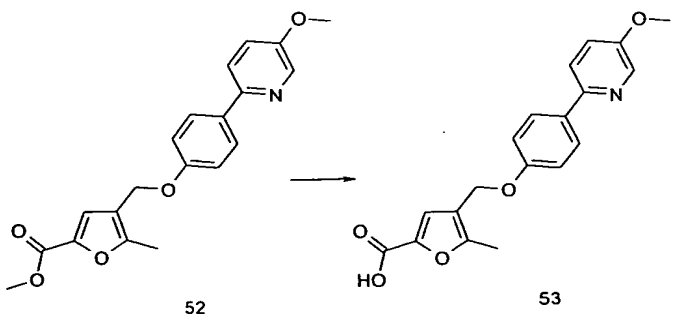
*(b) 4-[4-(5-Methoxy-pyridin-2-yl)-phenoxymethyl]-5-methyl-furan-2-carboxylic acid methyl ester (**52**)*



51 52

A mixture of 5-methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxymethyl]-furan-2-carboxylic acid methyl ester (**51**) (126mg), 2M aqueous cesium carbonate (0.6mL) and 2-iodo-5-methoxypyridine (95mg) in 1,4-dioxan (10mL) under an argon atmosphere was sonicated to expel traces of oxygen. [1,1'-Bis-(diphenylphoshino) ferrocene] dichloropalladium (II) (8mg) was added and the mixture heated at 95°C for 18 hours. After cooling, the mixture was acidified to pH6 with 1M aqueous hydrochloric acid and partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and evaporated to give compound **52** as an oil (70mg), which was used directly in the next step. LC/MS System A: R_t = 3.23 mins, m/z = 354 ((M+H) for $C_{20}H_{19}NO_5$).

*(c) 4-[4-(5-Methoxy-pyridin-2-yl)-phenoxymethyl]-5-methyl-furan-2-carboxylic acid (**53**)*



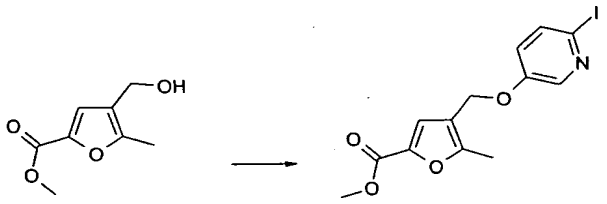
52 53

A mixture of 4-[4-(5-methoxy-pyridin-2-yl)-phenoxymethyl]-5-

methyl-furan-2-carboxylic acid methyl ester (**52**) (70mg) and 1M aqueous lithium hydroxide (1mL) in tetrahydrofuran/methanol (2:1 by volume) (12mL) was stirred at room temperature for 16 hours. The reaction mixture was acidified to between pH6 and pH7, and partitioned between ethyl acetate and water. The organic phase was separated, washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was purified by HPLC (gradient elution starting at 20% acetonitrile (containing 0.1% trifluoroacetic acid) 80% water (containing 0.1% trifluoroacetic acid) and increasing the acetonitrile phase at a rate of 1% per min. Compound **53** was obtained as a solid (2.5mg). LC/MS System A: R_t = 2.90 mins, m/z (ES^+) = 340 ((M+H) for $C_{19}H_{17}NO_5$).

Example 17: Synthesis of 4-[6-(4-Methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-furan-2-carboxylic acid (56)

*(a) 4-(6-iodo-pyridin-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**54**)*

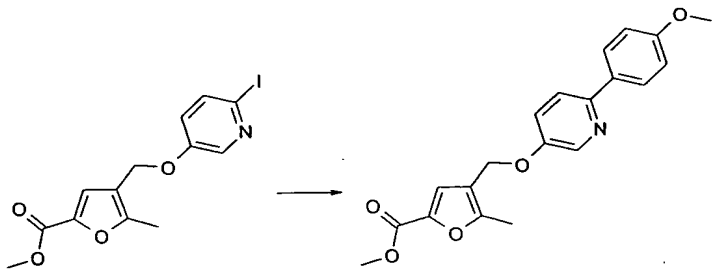


16 54

To a stirred solution of 4-hydroxymethyl-5-methyl-furan-2-carboxylic acid methyl ester (**16**) (100mg) and 5-hydroxy-2-iodo-pyridine (130mg) in dry tetrahydrofuran (5mL) was added triphenylphosphine (170.5mg) followed by drop-wise addition of di-isopropylazodicarboxylate (131mg) during 5 minutes. The mixture was stirred at room temperature for 16 hours. 4Å molecular sieve (8beads) was added, followed by additional aliquots of triphenylphosphine (170.5mg) and di-

isopropylazodicarboxylate (131mg) and stirring was continued for 1h. The mixture was evaporated and the residue partitioned between ethyl acetate and water. The organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent afforded an oil which was purified by flash chromatography (diethyl ether/petrol ether 1:1 v/v as eluent) to give compound **54** as a solid. LC/MS System A: R_t = 3.52 mins, m/z = 374 ((M+H) for $C_{13}H_{12}INO_4$)

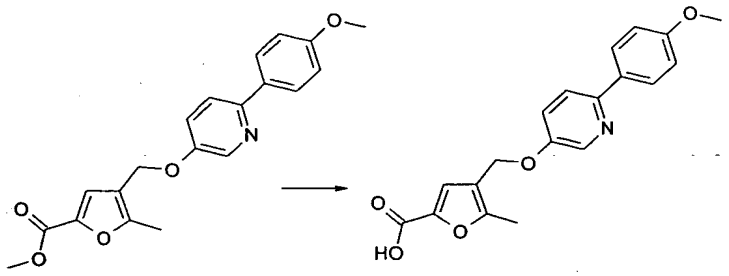
*(b) 4-[6-(4-Methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-furan-2-carboxylic acid methyl ester (**55**)*



54 55

A mixture of 4-(6-iodo-pyridin-3-yloxymethyl)-5-methyl-furan-2-carboxylic acid methyl ester (**54**) (50mg), 4-methoxyphenylboronic acid (40.7mg) and potassium acetate (30mg) in dry dimethylformamide (3.6mL) under an argon atmosphere was sonicated to remove traces of oxygen, then treated with [1,1'-bis-(diphenylphoshino) ferrocene] dichloropalladium (II) (10mg). The mixture was stirred and heated at 100°C for 16hours. After concentrating, the residue was partitioned between ethyl acetate and water, and the organic phase washed with brine and dried ($MgSO_4$). Evaporation of the solvent afforded compound **55** as a gum. This was used without further purification. LC/MS System A: R_t = 3.37 mins, m/z = 354 ((M+H) for $C_{20}H_{19}NO_5$).

(c) 4-[6-(4-Methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-furan-2-carboxylic acid ***(56)***



55 56

Compound **56** was prepared from 4-[6-(4-methoxy-phenyl)-pyridin-3-yloxymethyl]-5-methyl-furan-2-carboxylic acid methyl ester (**55**) (150mg) in an analogous manner to that described in Example 16(c), as a solid (2.5mg). LC/MS System A: R_t = 2.79 mins, m/z (ES^+) = 340 ((M+H) for $C_{19}H_{17}NO_5$)

Example 11: Biological Results

Binding ability to human EP receptors

Membranes were prepared from cells stably transfected with human EP receptor cDNA. In brief, cells were cultured to confluency, scraped from culture flasks, and centrifuged (800 g, 8 minutes, 4°C). Cells were twice washed in ice cold homogenisation buffer containing 10 mMTris-HCl, 1 mM EDTA.2Na, 250 mM sucrose, 1 mM PMSF, 0.3 mM indomethaicn, pH 7.4, homogenised and re-centrifuged as before. The supernatant was stored on ice and pellets re-homogenised and re-spun. Supernatants were pooled and centrifuged at 40000g, 10 minutes, 4°C. Resultant membrane pellets were stored at -80°C until use.

For assay, membranes expressing human EP_4, EP_3, EP_2 or EP_1 receptors were incubated in Millipore (MHVBN45) plates containing assay buffer, radiolabelled [^{3}H]PGE_2 and 0.1 to 10 000 nM concentrations of compounds. Incubations were

performed at suitable temperatures and for suitable times to allow equilibrium to be reached. Non-specific binding was determined in the presence of 10uM PGE_2. Bound and free radiolabel was separated by vacuum manifold filtration using appropriate wash buffers, and bound radiolabel was determined by scintillation counting. Constituents of each of the buffers are included in table 1 below.

The affinity or pK_i of each compound for each receptor was calculated from the concentration causing 50% radioligand displacement (IC_{50}) using the Cheng-Prusoff equation:

$$Ki = \frac{IC_{50}}{1 + \left(\frac{radioligand\ concentration}{radioligand\ KD} \right)}$$

This approach follows that set out in Kenakin, T.P., Pharmacologic analysis of drug receptor interaction. Raven Press, New York, 2nd edition.

Table 1

Receptor		**EP_1**	**EP_3**	**EP_3**	**EP_4**
Protein / well		6.5µg	8µg	5µg	5µg
Final [^{3}H-PGE_2]		3.6nM	3nM	2.5nM	1nM
Buffer	**Assay**	10mM MES pH6.0; 10mM $MgCl_2$; 1mM EDTA, 3uM Indomethacin	10mM MES pH6.0; 10mM $MgCl_2$; 1mM EDTA	10mM MES pH 6.0; 10mM MgCl2; 1mM EDTA, 100uM GTP-gamma-S	10mM MES pH6.0; 10mM $MgCl_2$; 1mM EDTA, 3uM Indomethacin
	Wash	10mM MES pH6.0; 10mM $MgCl_2$	10mM MES pH6.0; 10mM $MgCl_2$	10mM MES pH 6.0; 10mM $MgCl_2$	10mM MES pH6.0; 1mM EDTA

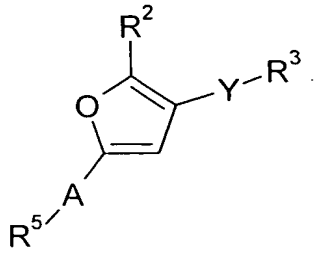
The results are presented as pK_i values in table 2 below.

Table 2

Compound	EP_4	EP_1	EP_2	EP_3
4	>6	<5	<5	<5
5	>7	<5.5	<5.5	<5
6	>8	<5	<5	<5
7	>6	<5	<5	<5
8	>8	<5	<5	<5
9	>8	<5	<5	<5
10	>8	<5	<5.5	<5
11	>8	<5	<5	<5
13	>8	<5	<5	<5
18	>5.5	<5	<5	<5
19	>6	<5	<5	<5
21	>6	<5	<5	<5
22	>8	<5	<5	<5
27	>6	<5	<5.5	<5
28	>6	<5	<5	<5
31	>5.5	<5	<5	<5
32	>5.5	<5	<5	<5
38	>6	<5	<5.5	<5
40	>7	<5	<5	<5
43	>7	<5	<5	<5
46	>7	<5	<5	<5
49	>8	<5	<5	<5
50	>5.5	<5	<5.5	<5
53	>5	<5	<5	<5
56	>5.5	<5	<5	<5

CLAIMS

1. A compound of formula (**I**):



(I)

or a pharmaceutically acceptable salt thereof for use in a method of therapy, wherein:

R^2 is H or an optionally substituted C_{1-4} alkyl group;

Y is either $-(CH_2)_n-O-$, where n is 1 or 2, or $-C(=O)NR^N-$, where R^N is selected from H, and optionally substituted C_{1-7} alkyl or C_{5-20} aryl;

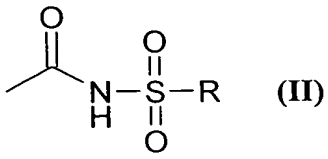
R^3 is an optionally substituted C_6 aryl group linked to a further optionally substituted C_6 aryl group, wherein if both C_6 aryl groups are benzene rings, there may be an oxygen bridge between the two rings, bound adjacent the link on both rings;

A is a single bond or a C_{1-3} alkylene group; and

R^5 is either:

(i) carboxy;

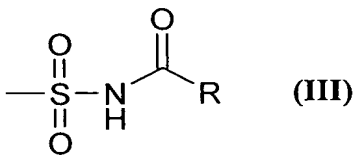
(ii) a group of formula (**II**):



(II)

; or

(iii) a group of formula (**III**):



(III)

,

wherein R is optionally substituted C_{1-7} alkyl or C_{5-20} aryl.

2. The compound according to claim 1, wherein R^2 is selected from H or methyl.

3. The compound according to either claim 1 or claim 2, wherein Y is $-(CH_2)_n-O-$.

4. The compound according to claim 3, wherein n is 1.

5. The compounds according to either claim 1 or claim 2, wherein Y is $-C(=O)NR^N-$.

6. The compound according to claim 5, wherein R^N is selected from H, and optionally substituted C_{1-4} alkyl.

7. The compound according to any one of the preceding claims, wherein the C_6 aryl groups of R^3 are independently selected from those derived from benzene and heteroaryl groups, where the heteroatom or heteroatoms are nitrogen.

8. The compound according to claim 7, wherein the C_6 aryl groups of R^3 are independently selected from those derived from benzene and pyridine.

9. The compound according to claim 8, wherein R^3 is optionally substituted biphenyl.

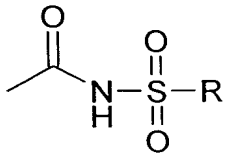
10. The compound according to claim 9, wherein R^3 is 4-phenyl-phenyl.

11. The compound according to any one of claims 1 to 10, wherein A is a single bond.

12. The compound according to any one of claims 1 to 10, wherein A is a C_{1-3} alkylene group.

13. The compound according to any one of the preceding claims, wherein R^5 is either:

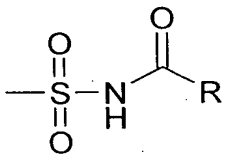
(i) a group of formula (**II**):



(**II**)

; or

(ii) a group of formula (**III**):



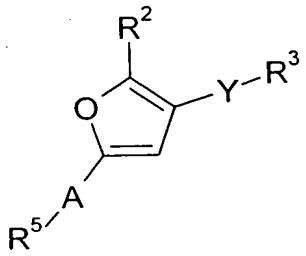
(**III**)

14. The compound according to claim 13, wherein R is selected from an optionally substituted C_{5-20} aryl group, and an optionally substituted C_{5-20} aryl-C_{1-7} alkyl group.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

16. The use of according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by antagonism of an EP_4 receptor.

17. A compound of formula (**I**):



(I)

or a salt, solvate and chemically protected form thereof, wherein:

R^2 is H or an optionally substituted C_{1-4} alkyl group;

Y is either $-(CH_2)_n-O-$, where n is 1 or 2, or $-C(=O)NR^N-$, where R^N is selected from H, and optionally substituted C_{1-7} alkyl or C_{5-20} aryl;

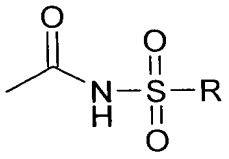
R^3 is an optionally substituted C_6 aryl group linked to a further optionally substituted C_6 aryl group, wherein if both C_6 aryl groups are benzene rings, there may be an oxygen bridge between the two rings, bound adjacent the link on both rings;

A is a single bond or a C_{1-3} alkylene group; and

R^5 is either:

(i) carboxy;

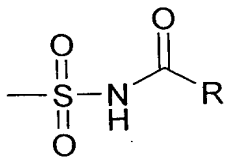
(ii) a group of formula (**II**):



(II)

; or

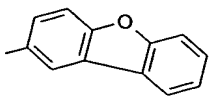
(iii) a group of formula (**III**):

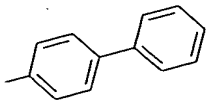


(III)

,

wherein R is optionally substituted C_{1-7} alkyl or C_{5-20} aryl, except that when R^2 is methyl, Y is $-CH_2-O-$ and R^5 is carboxy or C_{1-7} alkyl ester thereof, then R^3 is not:

(i)  ; or

(ii)  .